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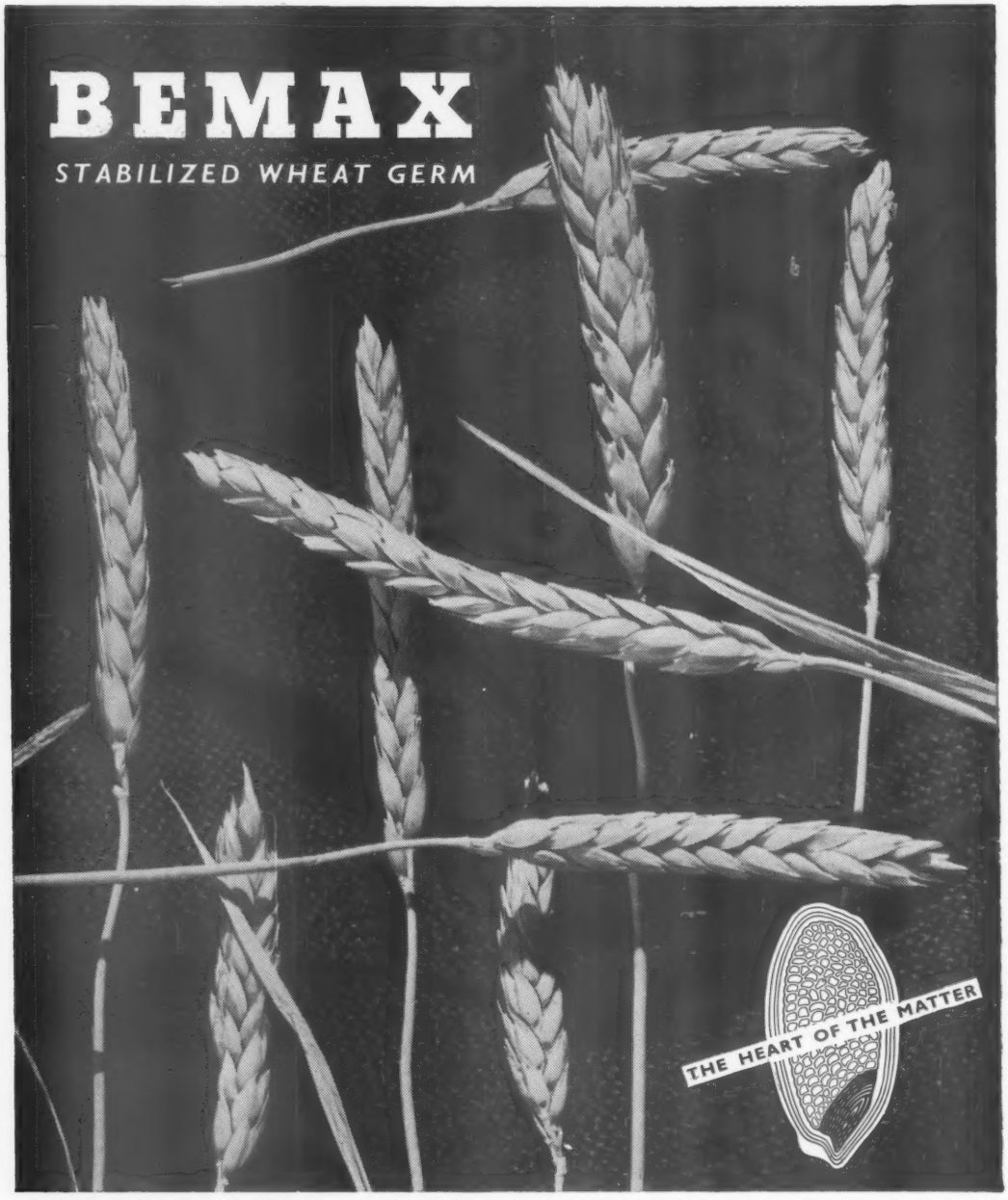

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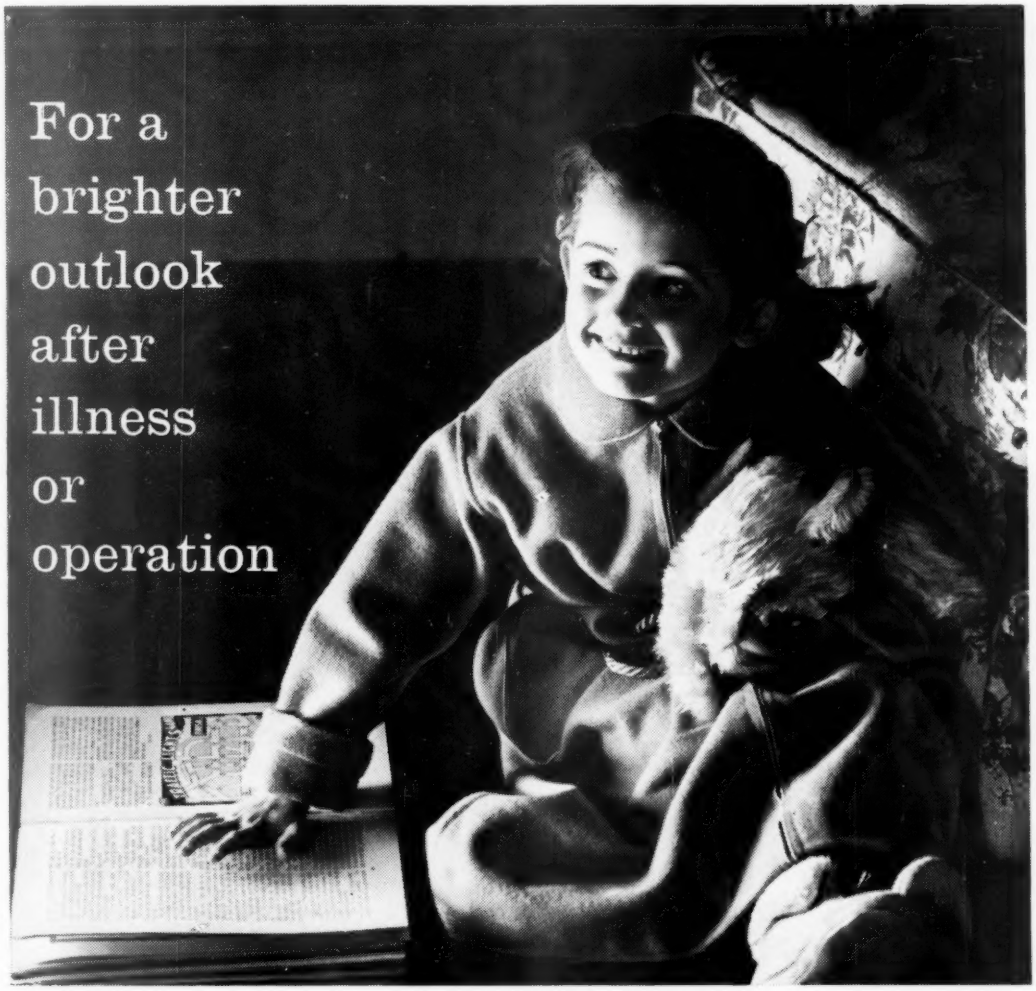

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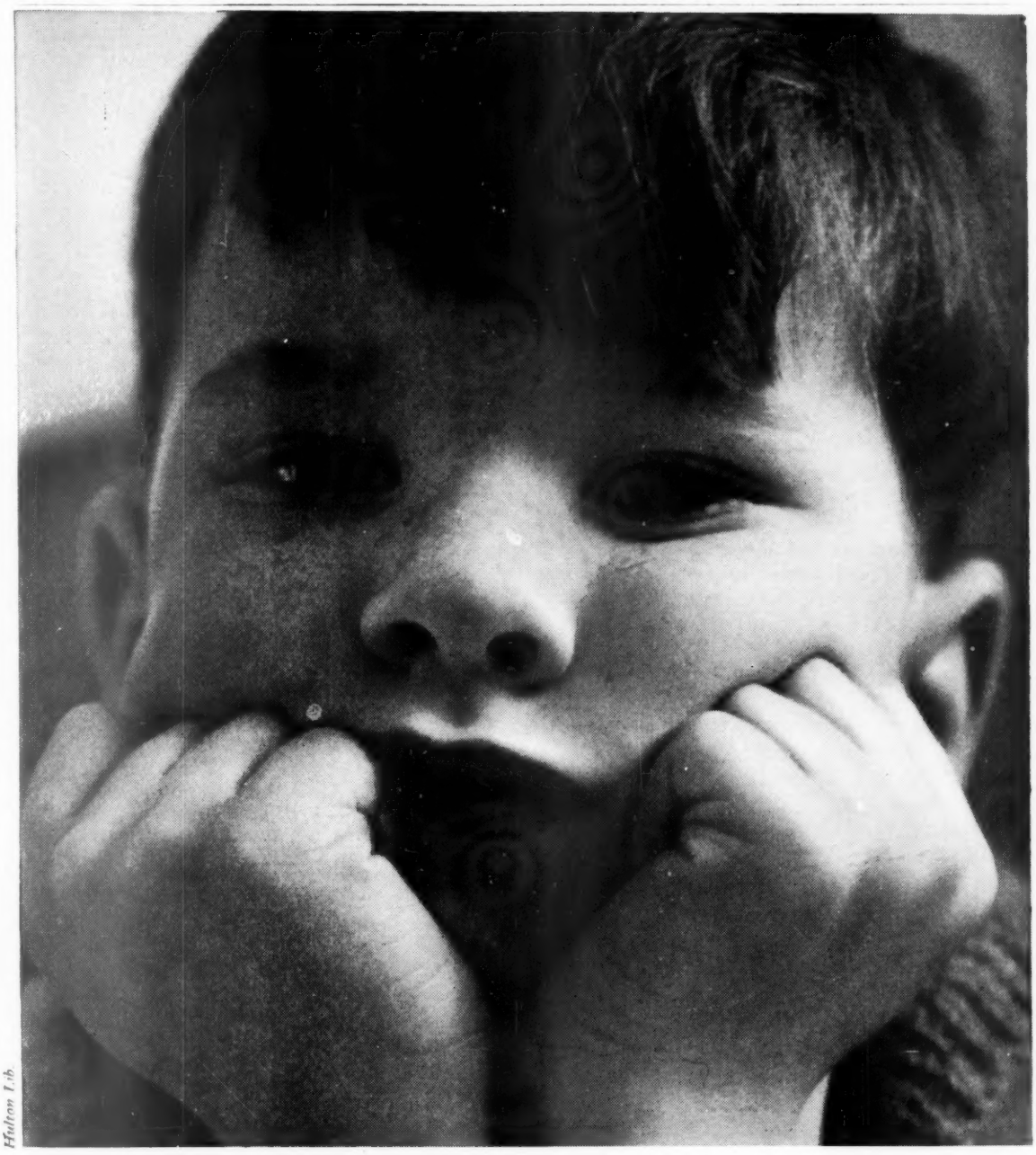

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SOME PHYSICAL MEASUREMENTS IN THE FIRST THREE YEARS OF LIFE

BY

FRANK FALKNER*

From the Child Study Centre, Institutes of Child Health and Education, University of London

(RECEIVED FOR PUBLICATION JULY 1, 1957)

There are few standards of physical measurements available for pre-school children in the British Isles. Gore and Palmer (1949) published cross-sectional data of the pre-school period based on measurements taken in 1947. Within each age-group sample there were differences of weeks or months between ages of individual children. The most recent publication of cross-sectional data in this age period was from the Oxford Child Health Survey in 1955 (Acheson, Kemp and Parfit, 1955) and gives standards of height and weight for children born between 1944 and 1948. This was a longitudinal study, but no incremental data were given. The late Professor Low's (1952) raw data have been published on several measurements for a group of children followed for the first five years of life and who were born between 1923 and 1927. So far as is known these are the only longitudinal data in this age period in the United Kingdom published up till now.

The following standards of children born between 1952 and 1954 are presented. For details of the sample, method of recruitment and investigations carried out, etc., reference may be made to Moore, Hindley and Falkner (1954). Briefly, the sample consists of 'healthy' unselected children, and these same children are followed regularly from birth. They are drawn from an area in London. The children are seen at the ages of 4 weeks (± 2 days), 13, 26, 39 weeks, 1 year, 18 months (± 7 days), 2 years and thence yearly (± 14 days). The majority of children are seen very close to the correct date and never outside these stated limits.

It may be remarked that at 3 years the number of children forming the sample drops considerably. At the time of analysis not all the original children had reached 3 years of age—a common happening in running analyses of longitudinal studies.

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Measurements

All the measurements were taken by one of four measurers, the majority being taken by one person, and the rest divided equally between the other three. All were trained. When a new measurer joined the team he or she was taught by a trained member, and checks of individual errors and variations were made from time to time. Lincoln (1930) has shown the very great improvement in accuracy after such training whereby important large errors are reduced to minimal ones.

Increments

Known gains in specific measurements are a valuable indication of rate of growth and progress. Krogman (1956) has said: 'It is a source of great weakness that this aspect of growth analysis is so consistently neglected.' Increments may be calculated only from children followed longitudinally and not from cross-sectional data. Increments presented in this paper are means calculated on children seen at the beginning and end of an incremental period. (Not all the children are able to present themselves for their appointed examinations every time.) 'Adjusted mean increments' will be given and the term needs explanation. It was clearly convenient to use 13 weeks as the standard comparative incremental period. Not all the intervals are 13 weeks; for example, 4 to 13 weeks is 9 weeks. These intervals were therefore 'adjusted' to bring them to a comparable 13-week period. This may not be entirely permissible, for it presumes that the rate of growth of the particular measurement is rectilinear at that time which may not, in fact, be so; but the periods between examinations are felt to be short enough to justify this where it has been necessary.

In presenting the increments of the children it might be argued that those children who were able to be included by virtue of being seen at the beginning and end of each incremental period, and

TABLE 1

MEAN RECUMBENT-LENGTH OF CHILD STUDY CENTRE CHILDREN AT 4 WEEKS TO 3 YEARS
(In inches to nearest 0·1 inch, and cm. to nearest mm. 1 S.D. of mean given)

Ages	Boys					Girls				
	No.	Inches		Cm.		No.	Inches		Cm.	
		Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.
4 wks.	82	21·2	0·9	53·9	2·3	77	20·7	0·7	52·5	1·8
13 wks.	96	23·7	0·9	60·2	2·4	85	22·9	0·6	58·2	1·6
26 wks.	94	26·3	0·9	66·7	2·4	81	25·5	0·8	64·8	2·6
39 wks.	84	28·1	1·0	71·3	2·6	78	27·3	1·0	69·3	2·6
1 yr.	80	29·5	1·1	75·0	2·7	78	28·9	1·0	73·3	2·6
18 mos.	77	32·0	1·2	81·2	3·2	66	31·4	0·9	79·7	2·4
2 yrs.	55	34·0	1·5	86·5	3·7	54	33·3	1·2	84·5	3·1
3 yrs.	28	37·1	1·9	94·1	4·8	21	37·0	1·4	94·1	3·4

thus more regularly, were not necessarily representative of the whole group. With this in mind, this possibility was examined and there was found to be no significant difference between the different groups, at the different ages, in size of recumbent-length, weight, crown–rump measurement or head circumference.

Length and Weight Measurements

Length. There is a difference in an individual's recumbent-length and standing height. Boyd (1929), on children aged 2–5 years, found differences of 1·0 to 1·5 cm., and with older children differences up to 3·0 cm. occur. Since children who can actually stand are not necessarily able to be stood erect in the correct position (Krogman, 1950), it is felt that measurement of standing height before the age of 3 years and possibly 4 is probably unreliable. All measurements of length in this series of children were taken with the child nude lying on a horizontal measuring table. Such tables have been developed by Todd at Western Reserve University, Thompson at Yale, Schultz at Johns Hopkins University and by Knott (1941), Hindley (1953), Thomson (1956) and Falkner (1957). The technique used is well summarized by Krogman (1950). The estimated maximum error was $\pm 0{\cdot}5\%$. Children were measured either in the morning or in the afternoon. Time of day is important in measuring height, for children can 'lose' 2 cm. in a day and 1 cm. can be lost in the first hour. This can be 'put back' again after a rest (Palmer, 1930; Redfield and Meredith, 1938; Boyd, 1929). This source of error is lessened in measuring recumbent-length, but at the same time the children were stretched (not severely) just before actual measurement.

Weight. All children were weighed in the nude to the nearest ounce on either a basket-scale or a platform beam balance (both periodically checked) according to age. Percentiles are given in the weight tables rather than standard deviations, for weight is not normally distributed (it is positively skewed), whereas recumbent-length is nearly so.

Figs. 1 and 2 show graphically* the data from Tables 1, 2, 3 and 4.

* In a study such as this there are several ways of plotting the data (Tanner, 1951), for not all the children are seen every time. Those that are at the beginning and the end of each incremental period only may be used to plot the velocity curve. Hence the distance curve can be plotted by using the maximum number of children seen at each age—in other words, using the longitudinal study cross-sectionally—or by plotting it from the velocity curve, having started with a mean size at birth or 4 weeks of age. (These are not the only ways (see Tanner, 1951), but the most simple, practical and least complicated.) All the distance curves plotted in this paper are from means at each age, but in each case curves were also plotted from the velocity data. On this sample of children both methods produced almost identical curves.

TABLE 2

MEAN 'ADJUSTED' INCREMENTS OF RECUMBENT-LENGTH OVER 13-WEEK PERIODS OF CHILD STUDY CENTRE CHILDREN FROM 4 WEEKS TO 3 YEARS

(In inches to nearest 0·1 inch, and cm. to nearest mm. 1 S.D. of mean given)

Ages	Boys					Girls				
	No.	Inches		Cm.		No.	Inches		Cm.	
		Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.
4–13 wks.	77	3·6	0·8	9·1	2·1	66	3·4	0·6	8·6	1·6
13–26 wks.	87	2·5	0·5	6·4	1·3	74	2·6	0·6	6·7	1·5
26–39 wks.	80	1·9	0·6	4·8	1·4	69	1·9	0·5	4·7	1·3
39 wks.–1 yr. ..	71	1·5	0·5	3·7	1·3	69	1·5	0·6	3·8	1·5
1 yr.–18 mos. ..	63	1·2	0·3	3·1	0·8	58	1·3	0·4	3·2	0·9
18 mos.–2 yrs. ..	51	1·0	0·3	2·6	0·7	45	1·0	0·2	2·6	0·6
2–3 yrs.	23	0·8	0·1	2·1	0·3	20	0·8	0·1	2·2	0·3

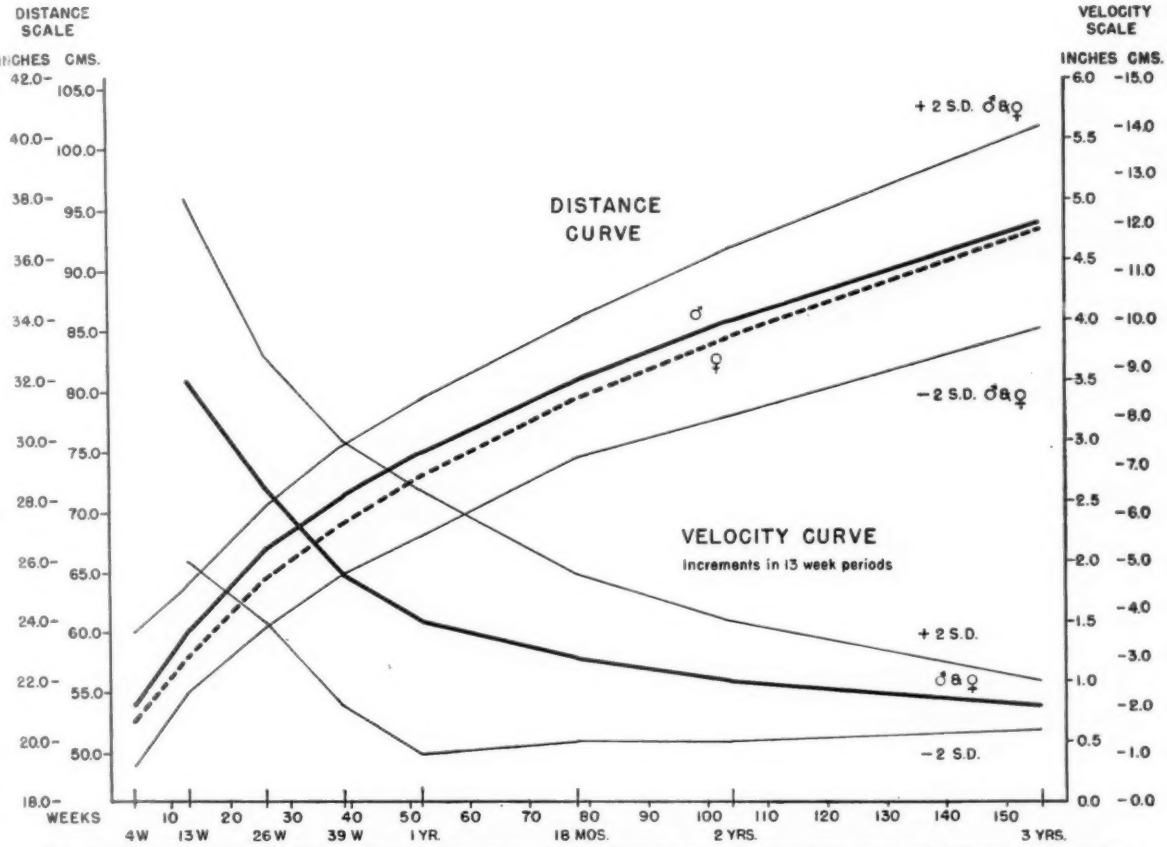

FIG. 1.—Recumbent-length: distance and velocity curves. In the distance curves, for simplicity, boys and girls are combined for ±2 S.D. curves. Boys and girls are combined to give the velocity curves, since their increments are so very similar.

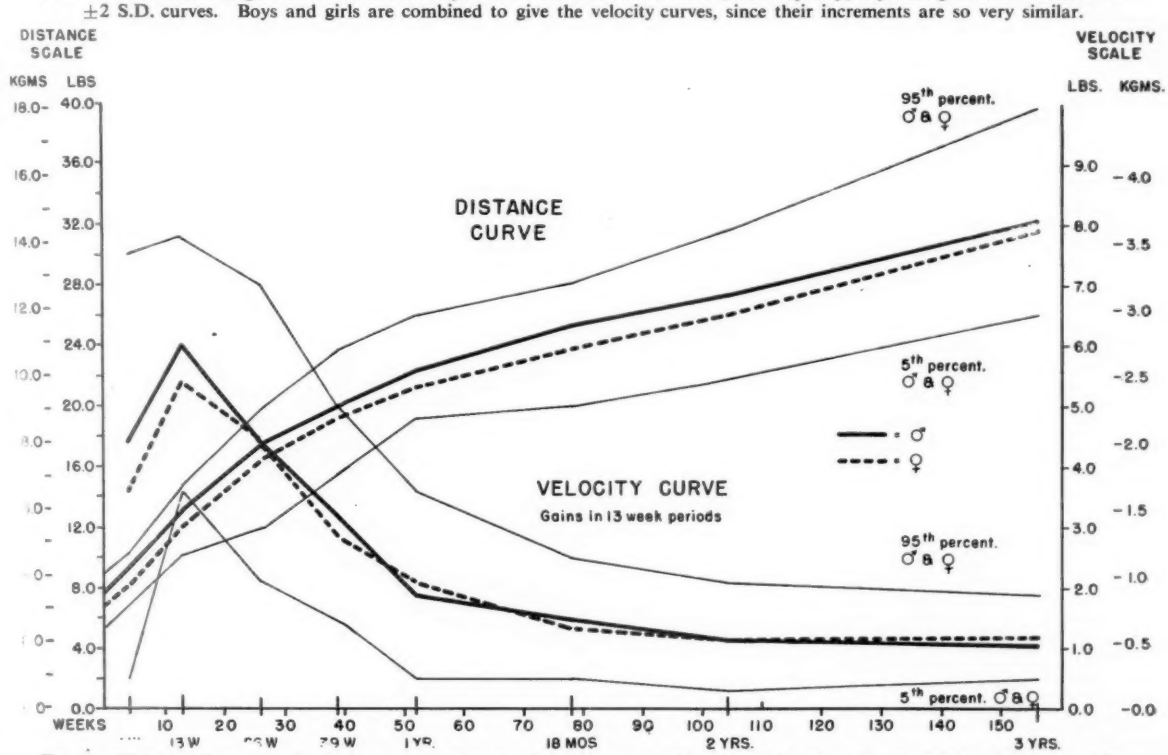

FIG. 2.—Weight: distance and velocity curves. For simplicity, boys and girls are combined to give the 95th and 5th percentiles.

TABLE 3

MEAN WEIGHT OF CHILD STUDY CENTRE CHILDREN AT BIRTH TO 3 YEARS

(In lb. to nearest 0·1 lb., and kg. to nearest 10 g.)

Boys

Ages	No. of Subjects	Percentiles							Mean Weight	
		1	5	20	50	80	95	99		
		Weight (lb.)							Lb.	Kg.
At birth	96	5·6	5·9	6·7	7·7	8·4	9·5	11·2	7·6	3·46
4 wks.	82	6·4	7·0	7·9	9·1	9·9	10·8	12·2	8·9	4·05
13 wks.	96	7·8	10·8	11·6	12·9	14·6	15·7	16·9	13·1	5·91
26 wks.	94	10·9	14·6	16·0	17·6	19·0	19·9	21·9	17·4	7·91
39 wks.	84	13·0	16·3	18·6	20·9	22·4	24·1	26·6	20·4	9·25
1 yr.	81	14·6	17·0	20·3	23·0	24·5	26·3	27·0	22·4	10·15
18 mos.	74	18·9	20·1	22·8	25·9	27·7	28·5	30·4	25·4	11·50
2 yrs.	57	21·7	22·0	25·3	27·6	30·1	31·9	32·6	27·5	12·48
3 yrs.	33	25·0	25·1	27·7	32·6	35·4	39·5	50·2	32·2	14·60

Girls

Ages	No. of Subjects	Percentiles							Mean Weight	
		1	5	20	50	80	95	99		
		Weight (lb.)							Lb.	Kg.
At birth	93	4·6	5·1	6·2	7·2	8·0	8·8	9·4	7·1	3·23
4 wks.	77	6·2	6·5	7·4	8·2	9·1	9·7	10·7	8·2	3·73
13 wks.	84	8·4	9·5	10·9	12·2	13·0	13·7	14·7	11·9	5·39
26 wks.	81	12·6	13·1	14·7	16·5	17·9	19·7	21·0	16·4	7·43
39 wks.	78	14·0	14·8	17·1	19·3	21·2	23·6	25·7	19·2	8·69
1 yr.	78	15·8	17·4	19·2	21·0	23·1	25·9	26·9	21·3	9·64
18 mos.	67	18·6	19·8	21·9	23·9	26·2	28·0	31·3	23·9	10·85
2 yrs.	57	20·8	21·5	23·6	25·8	28·3	31·3	32·6	26·1	11·81
3 yrs.	22	24·1	27·2	28·8	30·9	34·3	40·3	43·3	31·8	14·43

TABLE 4

'ADJUSTED' MEAN INCREMENTS OF WEIGHT GAIN OVER 13-WEEK PERIODS OF CHILD STUDY CENTRE CHILDREN FROM BIRTH TO 3 YEARS

(In lb. to nearest 0·1 lb., and kg. to nearest 10 g.)

Boys

Ages	No. of Subjects	Percentiles							Mean Increments	
		1	5	20	50	80	95	99		
		Increments (lb.)							Lb.	Kg.
Birth–4 wks.	73	−2·2	0·3	2·8	4·5	5·9	8·2	9·7	4·4	2·00
4–13 wks.	77	3·0	4·1	4·8	5·7	7·4	8·4	12·2	6·1	2·74
13–26 wks.	87	1·3	2·1	3·4	4·4	5·4	6·8	7·5	4·4	2·01
26–39 wks.	80	0·7	1·5	2·4	3·1	4·1	4·9	7·2	3·2	1·45
39–52 wks.	72	−1·3	0·2	1·2	2·0	2·4	3·8	4·3	1·9	0·86
1 yr.–18 mos.	60	−0·05	0·6	0·9	1·4	2·0	2·4	2·6	1·5	0·66
18 mos.–2 yrs.	51	0·2	0·5	0·7	1·2	1·5	2·1	2·4	1·2	0·53
2–3 yrs.	29	0·3	0·5	0·8	1·1	1·3	1·7	2·4	1·1	0·49

Girls

Ages	No. of Subjects	Percentiles							Mean Increments	
		1	5	20	50	80	95	99		
		Increments (lb.)							Lb.	Kg.
Birth–4 wks.	72	−1·2	0·7	2·1	3·5	5·0	6·8	7·8	3·6	1·64
4–13 wks.	65	2·5	3·2	4·3	5·1	6·7	7·2	8·4	5·3	2·42
13–26 wks.	73	1·1	2·1	3·3	4·4	5·8	7·2	7·6	4·5	2·05
26–39 wks.	69	0·2	1·3	2·0	2·6	3·9	5·4	6·0	2·9	1·30
38–52 wks.	69	0·1	0·9	1·4	2·0	2·7	3·4	4·4	2·1	0·93
1 yr.–18 mos.	59	−0·2	0·3	0·9	1·3	1·9	4·6	3·0	1·4	0·62
18 mos.–2 yrs.	48	−0·4	0·2	0·7	1·2	1·7	2·1	2·4	1·2	0·53
2–3 yrs	21	0·5	0·6	0·7	1·0	1·4	2·2	2·7	1·2	0·52

Discussion. While it is well known that boys are taller and heavier than girls, it is interesting to see how closely similar they are in increments (rate of growth) of recumbent-length and weight in this age period, except in the case of weight gain between birth and 3 months. Their birth weight and early recumbent-length differences are maintained.

From other studies (example: Simmons, 1944) it appeared that the size of the newborn baby is not related strongly to his size at, say, 2 years, and Tanner, Healy, Lockhart, MacKenzie and Whitehouse (1956) have shown that birth size is only very slightly related to adult size. It would seem that the genetically determined factor in the growth pattern of the child does not start to become evident until after 1 year of age and is quite apparent at 2 years, presumably the prenatal environmental influences having now been mainly eliminated. Tanner found a high relationship between adult size and size at 3 years.

The London data were examined to verify this hypothesis. Since weight is subject so much to the vicissitudes of life in this period, recumbent-length only was examined.

To check the possible effect of illness on these assumptions the groups were subdivided into children who had been (*a*) ill and not hospitalized, (*b*) hospitalized and (*c*) not ill at all. The correlations remained almost identically the same. Table 5 shows there is little relationship between recumbent-length at 4 weeks and 1 year, but a close relationship between 1 year and 2 years.

TABLE 5

CORRELATIONS BETWEEN RECUMBENT-LENGTHS OF CHILD STUDY CENTRE CHILDREN AT 4 WEEKS AND 1 YEAR AND AT 1 YEAR AND 2 YEARS

	4 Weeks and 1 Year		1 Year and 2 Years	
	No.	r	No.	r
Boys and girls	124	0·30	120	0·83
Boys	60	0·19	51	0·84
Girls	64	0·54	69	0·80

Regarding rate of growth, increments of recumbent-length between 4–13 weeks and 1 year–18 months were examined for relationships. Table 6 shows there is a very low relationship and confirms Tanner's (1956) observation that rate and size seem practically independent.

The Oxford, Aberdeen and another London set of

TABLE 6

CORRELATIONS OF RECUMBENT-LENGTH INCREMENTS OF CHILD STUDY CENTRE CHILDREN BETWEEN 4–13 WEEKS AND 1 YEAR–18 MONTHS

	No.	r
Boys and girls	124	0·08
Boys	54	0·07
Girls	50	0·23

TABLE 7

MEAN COMPARATIVE LENGTHS

(In inches to nearest 0·1 inch)

Ages	London, 1926 (Myers, 1926)		Aberdeen (Low, 1952)		Oxford (Acheson *et al.*, 1955)		London, 1952 (Child Study Centre)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Birth	—	—	19·6	19·5	—	—	—	—
4 wks.	21·0	20·9	—	—	—	—	21·2	20·7
13 wks.	23·0	22·7	—	—	—	—	23·7	22·9
26 wks.	25·0	25·3	—	—	—	—	26·3	25·5
39 wks.	26·2	26·8	—	—	—	—	28·1	27·3
1 yr.	27·9	27·5	28·9	28·6	—	—	29·5	28·9
18 mos.	31·0	30·6	—	—	31·9*	31·1*	32·0	31·4
2 yrs.	32·4	32·1	32·9	32·9	34·0*	33·2*	34·0	33·3
2½ yrs.	34·0	33·4	—	—	35·6*	35·1*	—	—
3 yrs.	36·1	35·4	36·2	36·4	37·3*	36·7*	37·1	37·0

* Standing height.

TABLE 8

MEAN COMPARATIVE INCREMENTS IN LENGTH

(In inches to nearest 0·1 inch)

Ages	Boys			Girls		
	Aberdeen	Oxford	London, 1952	Aberdeen	Oxford	London, 1952
1 yr.–2 yrs.	1·0	—	1·1	1·1	—	1·1
18 mos.–2 yrs.	—	1·0*	1·0	—	1·0*	1·0
2–3 yrs. ..	0·8	0·8*	0·8	0·9	0·9*	0·9

* Standing height.

TABLE 9
MEAN COMPARATIVE WEIGHTS
(In lb. to nearest 0·1 lb.)

Ages	London, 1926 (Myers, 1926)		Aberdeen (Low, 1952)		London, 1947 (Gore and Palmer, 1949)		Oxford (Acheson *et al.*, 1955)		London, 1952 (Child Study Centre)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Birth ..	—	—	7·0	6·9	—	—	7·6	7·3	7·6	7·1
4 wks. ..	8·3	8·2	—	—	8·6	8·5	—	—	8·9	8·2
13 wks. ..	11·5	10·7	—	—	13·1	12·2	—	—	13·1	11·9
26 wks. ..	15·4	15·8	—	—	17·5	16·4	17·5	16·1	17·4	16·4
39 wks. ..	18·1	18·1	—	—	20·5	19·3	—	—	20·4	19·2
1 yr. ..	20·5	19·5	20·6	19·9	22·6	21·0	22·7	21·1	22·4	21·3
18 mos. ..	22·7	22·1	—	—	25·5	24·1	25·4	23·9	25·4	23·9
2 yrs. ..	26·5	25·0	25·2	24·6	28·3	26·9	27·8	26·1	27·5	26·1
2½ yrs. ..	28·2	24·7	—	—	30·8	29·5	29·9	28·6	—	—
3 yrs. ..	30·2	29·3	28·7	29·4	32·8	31·6	32·2	31·0	32·2	31·8

TABLE 10
COMPARATIVE MEAN INCREMENTS OF WEIGHT
(In lb. to nearest 0·1 lb.)

Ages	Aberdeen (Low, 1952)		London, 1947 (Gore and Palmer, 1949)		Oxford (Acheson *et al.*, 1955)		London, 1952 (Child Study Centre)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Birth–4 wks. ..	—	—	—	—	—	—	4·4	3·6
4–13 wks. ..	—	—	6·5	5·3	—	—	6·1	5·3
13–26 wks. ..	—	—	4·4	4·2	—	—	4·4	4·5
26–39 wks. ..	—	—	3·0	2·9	—	—	3·2	2·9
39 wks.–1 yr. ..	—	—	2·1	1·7	—	—	1·9	2·1
1 yr.–18 mos. ..	—	—	1·5	1·5	1·4	1·4	1·5	1·4
1 yr.–2 yrs. ..	1·2	1·2	1·4	1·5	1·3	1·2	1·3	1·2
18 mos.–2 yrs. ..	—	—	1·2	1·4	1·2	1·1	1·2	1·2
2–3 yrs. ..	0·9	1·2	1·1	1·2	1·1	1·1	1·1	1·2

children are compared in means in Tables 7 and 8. The Aberdeen and London data in Table 8 are true mean increments. The Oxford increments have been obtained by subtracting mean heights at the ages stated; they are thus an approximation only.

Comparative weights are given in Tables 9 and 10. Because of the arrangement of age groups in Table 10 the London 1926 data did not permit increments to be obtained. The London 1947 and Oxford 1948 increments in this table have been obtained by subtracting the means at the ages stated and are thus approximations; the Aberdeen and London 1952 increments are true increments.

Tables 7, 8, 9 and 10 show that, although the samples are not strictly comparable, the trend of children to become taller and heavier as time goes on is apparently maintained (Annotation in *Lancet*, 1955; Tanner, 1955). This is apparently due to the consistent biological fact that children are reaching physical maturity earlier and earlier. Skeletal maturity assessments upon the early samples of children would be most interesting had they been

TABLE 11
MEAN CROWN–RUMP MEASUREMENTS OF CHILD STUDY CENTRE CHILDREN AGED 4 WEEKS TO 3 YEARS
(In inches to nearest 0·1 inch, and cm. to nearest mm. S.D. = 1 standard deviation of mean)

Ages	Boys					Girls				
	No.	Inches		Cm.		No.	Inches		Cm.	
		Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.
4 wks.	82	13·8	0·7	35·0	1·7	77	13·7	0·5	34·3	1·3
13 wks.	95	15·4	0·7	39·2	1·7	84	14·9	0·5	37·9	1·2
26 wks.	94	17·0	0·6	43·3	1·6	81	16·6	0·5	42·1	1·3
39 wks.	84	18·0	0·7	45·8	1·8	77	17·5	0·6	44·5	1·5
1 yr.	79	18·7	0·6	47·5	1·6	77	18·2	0·8	46·2	2·0
18 mos.	85	19·8	0·7	50·2	1·8	75	19·4	0·7	49·3	1·9
2 yrs.	55	20·7	0·9	52·6	2·4	53	20·3	0·7	51·6	1·7
3 yrs.	31	22·2	1·1	56·3	2·7	26	21·6	1·1	54·9	2·7

available. The Oxford 1948 and London 1952 data are very similar. It is also apparent how very similar are all the incremental figures irrespective of the date of the study. Again, rate of growth and size have been suggested to be independent.

Other Measurements

Upper Segment (or Crown–Rump Length) and Lower Segment (or Lower-stem Length). The crown–rump measurement was obtained on the same measuring-board as for recumbent-length. The child's legs are raised vertically, the measurement representing the distance between the crown of the head and the rump over a line connecting the ischial tuberosities. (See Bean, 1922; Knott, 1941; Falkner, 1957, etc.) Results are given in Tables 11 and 12.

Lower-segment length is obtained by simple subtraction of crown–rump length from total recumbent-length. The ratio of upper to lower segment is a useful index of growth and is commonly expressed as the percentage of the total length that is made up by the upper segment. It is known as the stem-stature index, and is expressed as:

$$\frac{\text{Stem-length (crown–rump length)} \times 100}{\text{Recumbent-length (or height)}}$$

The maximum standard deviation of the mean at any age in the Aberdeen or London children (where the raw data were available) was $\pm 1 \cdot 6$.

The index varies remarkably little between some widely different samples and decreases with age, as the lower limbs grow more rapidly than the upper segment. It reaches its final adult stable figure at approximately 12 years in the female and 16 years in the male. At the third month of foetal life it is of the order of 80·0 (Schultz, 1926), and at birth indexes from different racial groups vary little between 66·0 and 67·5 (examples: Japanese—Ito,

TABLE 12

MEAN 'ADJUSTED' INCREMENTS OF CROWN–RUMP MEASUREMENT IN 13-WEEK PERIODS OF CHILD STUDY CENTRE CHILDREN AGED 4 WEEKS TO 3 YEARS
(In inches to nearest 0·1 inch, and cm. to nearest mm.)

Ages	Boys			Girls		
	No.	'Adjusted' Mean Increment		No.	'Adjusted' Mean Increment	
		Inches	Cm.		Inches	Cm.
4–13 wks.	76	2·4	6·1	65	2·2	5·5
13–26 wks.	86	1·6	4·0	73	1·7	4·2
26–39 wks.	80	1·0	2·6	68	0·9	2·4
39 wks.–1 yr.	70	0·7	1·7	66	0·7	1·8
1 yr.–18 mos.	70	0·5	1·4	66	0·6	1·6
18 mos.–2 yrs.	50	0·5	1·2	44	0·5	1·2
2–3 yrs.	25	0·4	1·1	24	0·3	0·8

TABLE 13

MEAN STEM-STATURE INDEX OF CHILD STUDY CENTRE CHILDREN COMPARED WITH OTHER CHILDREN

Ages	London, 1952		Aberdeen (Lowe, 1952)		Detroit (Hejinian and Hatt, 1929)		New York (Wallis, 1931)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Birth	—	—	67·8	68·1	—	—	—	—
4 wks.	65·0	65·2	—	—	—	—	—	—
13 wks.	65·0	65·1	—	—	—	—	—	—
26 wks.	64·8	64·9	—	—	—	—	—	—
39 wks.	64·1	64·0	—	—	—	—	—	—
1 yr.	63·3	63·0	63·1	63·3	—	—	63·6	62·8
18 mos.	61·7	61·7	—	—	—	—	—	—
2 yrs.	60·8	61·0	61·4	61·1	61·2	60·8	60·8	60·2
3 yrs.	59·7	58·3	59·9	59·2	59·3	59·2	58·8	58·4

TABLE 14

MEAN HEAD CIRCUMFERENCES OF CHILD STUDY CENTRE CHILDREN AGED 4 WEEKS TO 3 YEARS
(In inches to nearest 0·1 inch, and cm. to nearest mm.)

Ages	No.	Boys				No.	Girls			
		Inches		Cm.			Inches		Cm.	
		Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.
4 wks.	82	14·7	0·4	37·4	1·1	77	14·4	0·4	36·5	1·0
13 wks.	96	16·0	0·4	40·7	1·1	84	15·6	0·5	39·7	1·2
26 wks.	94	17·3	0·5	43·8	1·2	81	16·8	0·4	42·7	1·1
39 wks.	83	18·0	0·5	45·7	1·3	78	17·6	0·5	44·6	1·2
1 yr.	79	18·4	0·5	46·8	1·3	75	18·0	0·5	45·7	1·2
18 mos.	83	19·0	0·5	48·3	1·3	74	18·5	0·4	47·0	1·1
2 yrs.	58	19·4	0·6	49·3	1·4	57	18·8	0·4	47·9	1·1
3 yrs.	35	19·8	0·5	50·4	1·3	32	19·5	0·4	49·5	1·1

1936; American—Bakwin and Bakwin, 1934; Italian—Tatafiore, 1935). At 8 years it approximates 54·5 (Wallis, 1931). By puberty it is of the order of 51·5 to 52·0 in both sexes, and thereafter remains at this minimum amount. The index is influenced by age, sex, race and constitutional type. There are two areas of very low upper-segment length—Central Africa and Native Australasia; and two 'high' areas—Central Africa (Pygmies) and the Arctic (Bean, 1922); but otherwise the index appears remarkably stable and comparable in distribution.

Bean (1922) stated that in different samples the female index was generally larger than the male, regardless of constitutional type and stature. The present sample of children does not indicate that such differences appear in the first three years of life at least.

In certain diseases the index is altered and may give a useful additional diagnostic indication. As an example, in cretinism the dwarfism includes retardation of growth of the lower limbs, and this manifests itself in the index. Five cretins recently seen had the following indices: two aged 4 weeks—mean of 69·0; two aged 3 months—mean of 68·1; and one aged 6 months—66·9. By comparison with Table 13 it will be seen that these indices are high.

Head Circumference. This is taken with a flexible, narrow-width steel tape and represents the maximum circumference, with the tape passing round the occipital and frontal areas and held perpendicular to the mid-sagittal plane.

TABLE 15

'ADJUSTED' MEAN INCREMENTS OF HEAD CIRCUMFERENCE IN 13-WEEK PERIODS OF CHILD STUDY CENTRE CHILDREN AGED 4 WEEKS TO 3 YEARS

(In inches to nearest 0·1 inch, and cm. to nearest mm.)

Ages	Boys			Girls		
	No.	'Adjusted' Mean Increment		No.	'Adjusted' Mean Increment	
		Inches	Cm.		Inches	Cm.
4–13 wks.	77	1·9	4·8	65	1·9	4·8
13–26 wks.	87	1·2	3·1	73	1·2	3·1
26–39 wks.	79	0·8	2·0	69	0·7	1·9
39 wks.–1 yr.	69	0·5	1·2	67	0·4	1·1
1 yr.-18 mos.	67	0·3	0·7	62	0·3	0·7
18 mos.–2 yrs.	49	0·2	0·5	26	0·2	0·5
2–3 yrs.	33	0·1	0·3	28	0·1	0·4

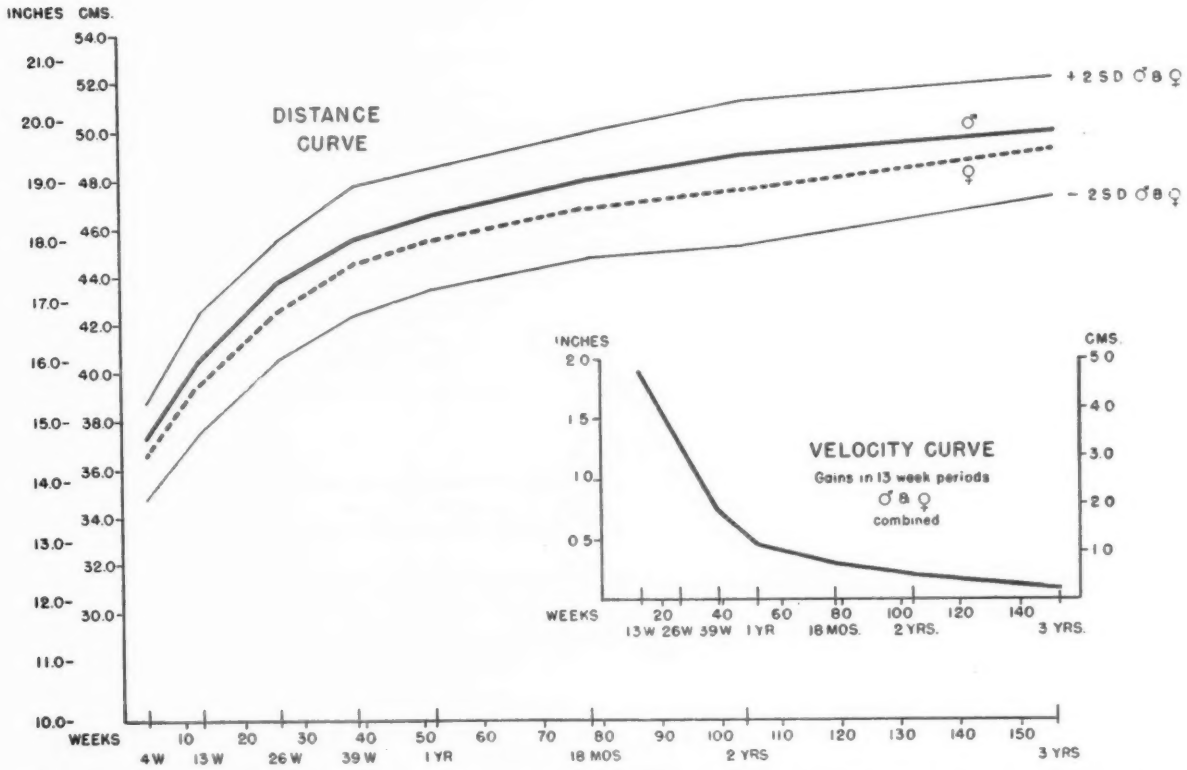

FIG. 3.—Head circumferences: distance and velocity curves. In the distance curves, for simplicity, boys and girls are combined to give the 2 S.D. curves. Boys and girls are combined to give the velocity curves, since their increments are almost identical.

Head circumference is a useful measurement clinically in early childhood, particularly when hydrocephalus, subdural haematoma or neoplasms are in question. Correlations between head measurement, cranial capacity and intelligence are, however, uniformly low and of the order of 0·12 (Broom, 1932; Paterson, 1930). Incremental data may be of most use. Although the boys' mean head circumferences are consistently larger than the girls', the mean increments are practically identical.

Fig. 3 shows graphically* the data from Tables 14 and 15. The incremental curve is of boys and girls combined.

Summary

Means and mean increments of recumbent-length, weight, crown–rump length and head circumference are given for children from a longitudinal developmental study in London. The children were born in 1952–4. Standard deviations and percentiles are given. Comparative lengths and weights, and increments of both, are given for samples of children born from 1923 to 1954. The secular trend for children to become larger continues. The relationship between early, late and adult life is discussed. There is very little relationship between size at 4 weeks and 1 year, but a good relationship between 1 year and 2 years. Size appears independent of rate of growth, which shows little relationship from any age to any age. Stem-stature indices are given and comparisons with other samples made. Their usefulness is discussed.

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* See footnote on page 2.

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GROWTH AND DEVELOPMENT IN A GROUP OF CHILDREN OF VERY LOW BIRTH WEIGHT

BY

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In recent years improved techniques in premature baby care have resulted in a greatly improved expectation of life for the very small, premature baby. Table 1 gives the survival rates from one large Edinburgh maternity hospital for six premature weight groups in the years 1945 and 1954. It will be seen that the most striking improvement is found in the lowest weight groups. This raises the important question of what happens to these very small babies in later life. Although there is an extensive literature on the growth and development of premature babies, the majority of investigators have considered premature babies as a whole, *i.e.*, all those with a birth weight of 5½ lb. (2,500 g.) or less, the samples studied being heavily weighted by the larger premature infants. A recent survey of all premature births in Edinburgh, in the years 1952 to 1953 (Drillien and Richmond, 1956), showed that 57% of all births registered as being premature by weight were between 4 lb. 9 oz. and 5 lb. 8 oz. at birth. In another investigation (Drillien, 1957), it was shown that amongst primiparae 49% of babies considered premature on a weight basis were reported as having a gestation time of 38 weeks or longer; the comparable figure amongst higher parities was 37%. The majority of these small, full-time babies weighed between 5 and 5½ lb. at birth, and practically all of them were over 4½ lb. (2,041 g.).

TABLE 1

SURVIVAL RATES FOR BABIES OF 5½ LB. AND UNDER AT BIRTH IN ONE EDINBURGH MATERNITY HOSPITAL

Weight in lb.	Percentage Survival	
	1945	1954
5 to 5½ ..	91·6	96·3
4½ to 5 ..	83·3	84·6
4 to 4½ ..	81·6	82·4
3½ to 4 ..	51·8	71·4
3 to 3½ ..	35·0	73·0
Under 3 ..	4·5	28·2

It appears, therefore, that the effect of prematurity on later growth and development may be seriously underestimated if the sample studied contains an undue proportion of small but mature infants.

Hess and Lundeen (1949) in their book, 'The Premature Infant', describe briefly a follow-up investigation of 259 infants born between 1922 and 1947 whose birth weights varied from 735 to 1,260 g. (1 lb. 10 oz. to 2 lb. 8 oz.). Two hundred and twelve (82%) were traced and examined. These cases were graded as to physical and mental development: 48% were considered to be of average physical development and 59% of average mental development. Unfortunately no details are given of the criteria of normality used.

Howard and Worrell (1952) quote a personal communication from Hess regarding the progress of 317 children who were then 8 years or older, of birth weight between 605 and 1,260 g. (1 lb. 5 oz. to 2 lb. 8 oz.). Of these, 51% were considered to be of normal physical status and 64% of average mental development, figures closely paralleled by the previous investigation.

Kunstadter and Bartelme (1934) describe in detail the findings in 17 children surviving a birth weight of less than 1,000 g. (2 lb. 3 oz.). Of these, five died after discharge from hospital and before the age of 2 years. Developmental testing was carried out on 10 of the children: five were considered to be of normal or superior intelligence, and five definitely retarded. Out of eight cases, in which reports were given as to emotional stability, four were regarded as having marked behaviour problems, two as having minor behaviour problems and two were said to be stable and emotionally mature. Nine children over the age of 1 year were weighed and measured: eight were found to be underweight, most of them considerably so. These eight children were also retarded in height, but not to the same extent as in weight.

Knobloch, Rider, Harper and Pasamanick (1956) describe the findings in 57 infants at 9 months of

age, whose birth weight was 1,500 g. (3 lb. 4 oz.) or less, this being a part of a wider study of premature infants of different birth weights. They considered that in this low birth weight group 44% of the infants had an abnormal condition of sufficient magnitude to cause serious concern about the prognosis for future development. The comparable incidence for the rest of the premature infants was 8·6% and for full-term infants 2·6%.

Method of Investigation

A long-term study of the growth and development of premature and mature infants, born in Edinburgh hospitals between the years 1953 and 1955, yielded 20 children whose weight was 3 lb. or less at birth. In view of the small number it was decided to continue to follow up all cases in this low birth weight group born after 1955, and also to go back over a period of years in order to collect a larger number of these children. In all a total of 75 names was obtained. In every case the family has been traced, and in all but one where the family had moved out of the district, the mother has been interviewed and living children examined.

Table 2 gives the numbers of children by age of the last examination. It will be noticed that there are nearly twice as many girls as boys in this sample, due no doubt to their slightly longer gestation time for any given birth weight, associated with the fact that girls withstand the hazards of birth better than boys of like weight. All cases of 3 years and under are included in the larger survey and are seen at regular six-monthly intervals. Over this age the children have been seen on one or two occasions only. Five children died before the age of 2 years.

TABLE 2
COMPOSITION OF THE SAMPLE

Age	Total	Boys	Girls
6 months	5	1	4
1 year	4	1	3
1½ years	5	1	4
2 years	12	4	8
2½ years	1	–	1
3 years	10	6	4
4 to 5 years ..	12	5	7
5 to 6 years ..	5	1	4
6 to 7 years ..	7	2	5
7 to 8 years ..	3	–	3
8 to 9 years ..	5	2	3
Total	69	23	46

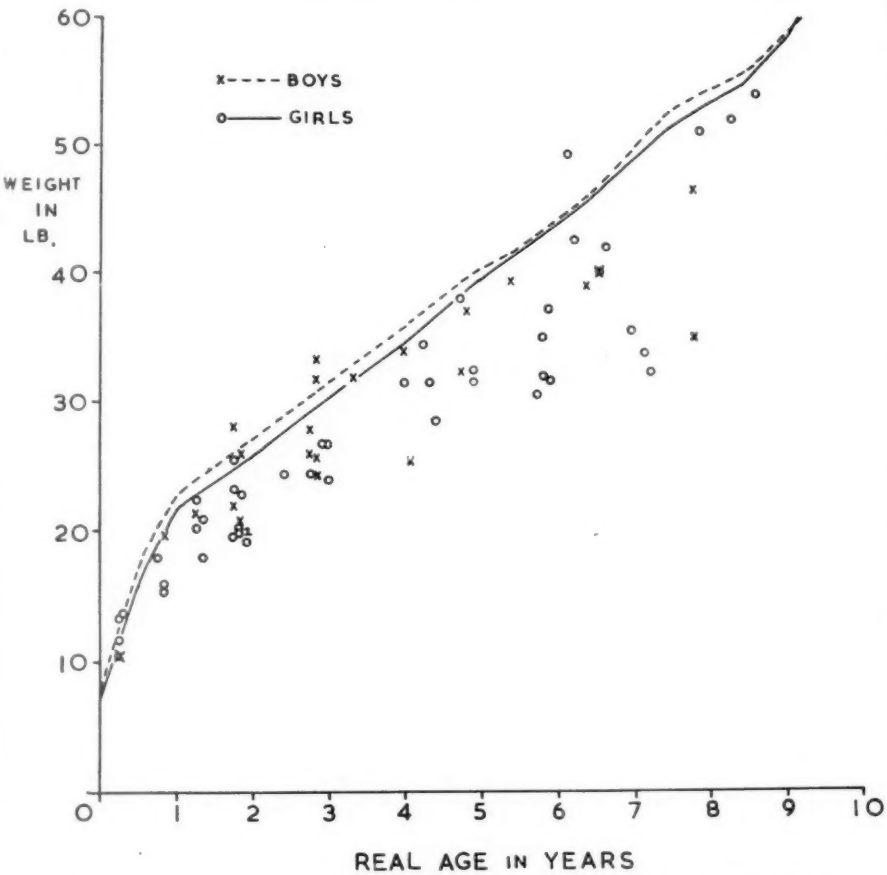

FIG. 1.– Weights of prematurely born children compared with mean weights of normal children.

In one case the child died at 18 months, the cause of death being bronchopneumonia. In the other four cases, in which death occurred at 6 months or earlier, the cause of death was not known. In two cases the child was found dead in the cot, having been apparently quite well a few hours earlier. In the other two cases, the child appeared fretful and refused feeds in the evening and died the following morning before medical aid was summoned.

Physical Development

The children were weighed in light, indoor clothes without shoes,

and an appropriate deduction was made for the amount of clothing still worn. All children of 2 years and over were measured recumbent, without shoes, on a portable measuring board.

Normal weight and length curves were constructed from means for Edinburgh infants, pre-school and school children (1951 to 1956) given in 'Disease in Infancy and Childhood' Ellis (1956).

In the accompanying figures the weeks of prematurity have been deducted from the chronological age to give the real age.

Fig. 1 gives the weights of 69 children, 46 girls and 23 boys, at the time of their last examination. Except in the first six months of life almost all are underweight, many considerably so, even when allowance is made for the degree of prematurity.

Fig. 2 shows the lengths of 54 children, 35 girls and 19 boys. The retardation in length is not so marked as for weight. This is demonstrated in Fig. 3, where curves have been constructed from the figures used previously for normal weight and length, giving the expected ratio of weight to length. It will be seen that many of the premature children are markedly underweight for their height, as well as being generally small for their age.

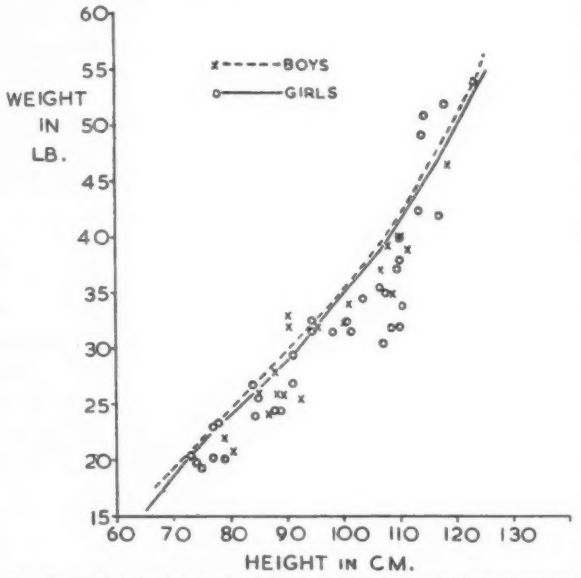

FIG. 3.—Height/weight ratios in prematurely born children compared with those for normal children.

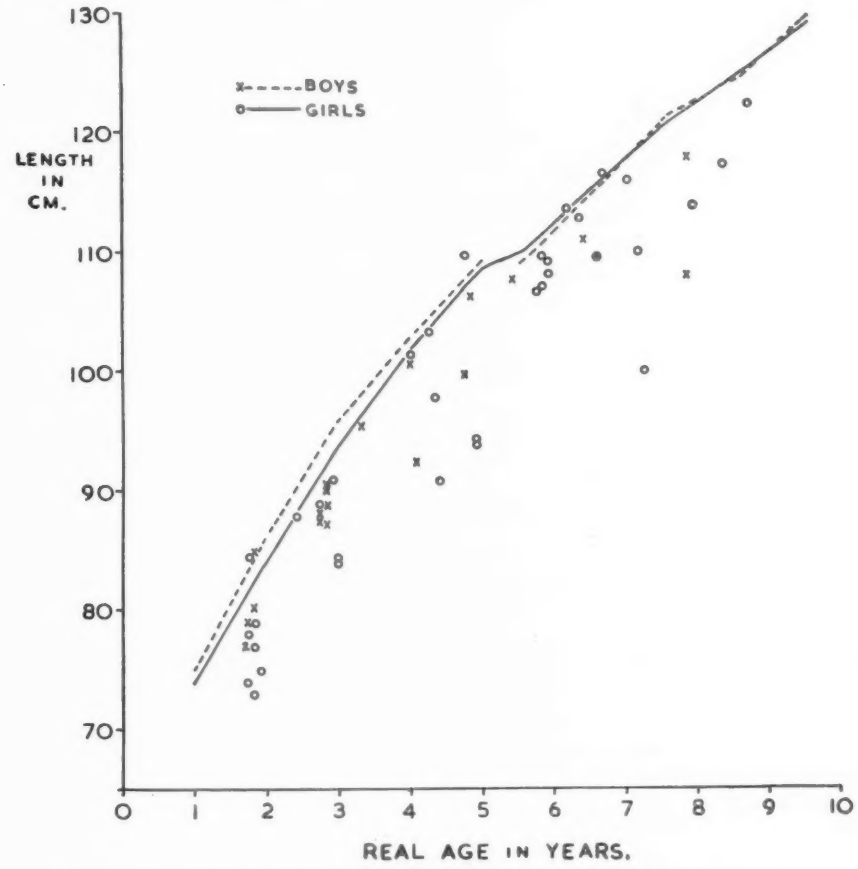

FIG. 2.—Lengths of prematurely born children compared with mean lengths of normal children.

Figs. 4 and 5 present the same data in a different way. For every case, excepting those of 6 months and younger, the ratio is given, expressed as a percentage, of the 'weight age' to the real age of the child, the 'weight age' being the age at which a 'normal' child would have the weight of the child in question. For children of 2 years and over, a similar ratio has been calculated of 'length age' to real age. Again allowance has been made for degree of prematurity. The data are summarized in Table 3. The figures show that there is no apparent tendency for physique to improve with age, the proportion of undersized children remaining steady throughout the age period under review.

Mental Development

All children of 3 years and under were given developmental tests based on those described by Gesell (1941, 1950). It was not possible to carry out the complete battery of tests in every case, but in the majority information has been obtained as to ability in locomotor activities, hand manipulation, language and social adjustment. These cases are included in the larger survey and have been tested at regular six-monthly intervals. For each case the developmental quotient (D.Q.) has been calculated.

The D.Q. is the relationship between 'maturity age' and actual age, expressed as a percentage value.

$$\text{D.Q.} = \frac{\text{Maturity age}}{\text{Chronological age} - \text{weeks of prematurity}} \times 100$$

Children over the age of 3 years were tested on the Terman Merrill L. test. In those cases where the child was markedly retarded, Gesell tests were used up to the 3-year level, and Terman Merrill tests also used if the child showed an average result, at the 3-year level, on the Gesell tests.

In assessing the mental development of the school age group much assistance has been given by the school medical officers, who either obtained a report from the child's class teacher, or arranged for the child to be given an I.Q. test. Five children in this group are attending the Royal Blind School, Edinburgh, and an assessment of intelligence was supplied by the Headmaster.

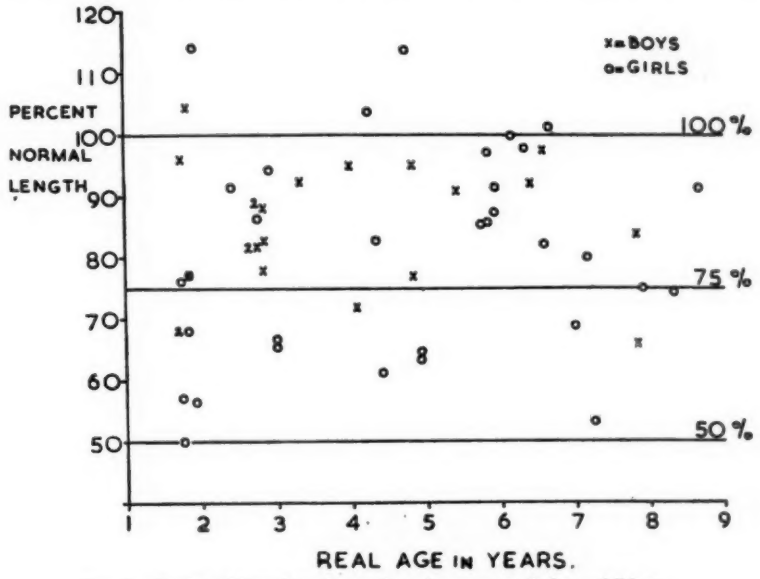

FIG. 5.—Ratios of 'length age' to real age in prematurely born children.

TABLE 3
RATIO OF WEIGHT AND LENGTH AGES TO REAL AGE IN PREMATURE GROUP

Ratio of Weight and Length Ages to Real Age (%)	Weight	Length
100 or over	5 (7·8%)	6 (11·3%)
76 to 100	19 (29·7%)	32 (60·4%)
51 to 75	32 (50·0%)	15 (28·3%)
50 or less	8 (12·5%)	—
Total	64 (100 %)	53 (100 %)

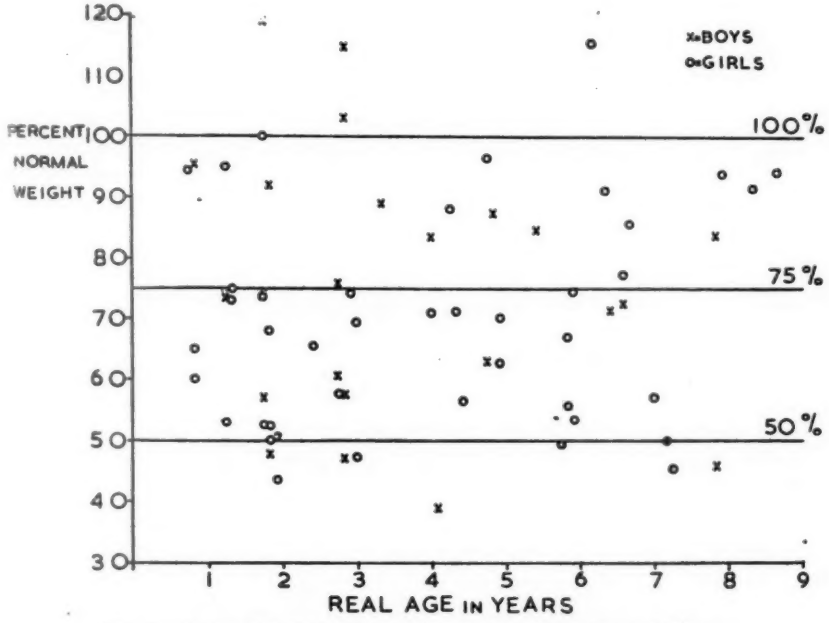

FIG. 4.—Ratios of 'weight age' to real age in prematurely born children.

Mental Development in the Pre-School Period

Fig. 6 gives the D.Q. for 38 children, 22 girls and 16 boys, between the ages of 1 and 5 years. Only 14 children (37%) have a D.Q. of 90 or over. These

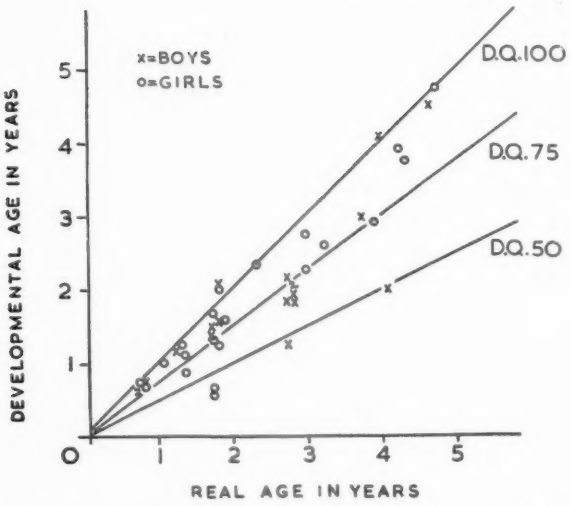

FIG. 6.—Developmental quotients for 38 pre-school prematurely born children.

can be considered normal, or superior in mental ability. Thirteen children (34%) have a D.Q. between 75 and 89, and are definitely dull; seven (18%) between 50 and 74 may be considered high-grade defectives; and four (11%) below 50 as grossly defective.

The children of 3 years and under, who are included in the larger survey, have been compared with other children in the survey of different birth weights. In each case the child included in this study has been matched with others of like age and sex selected at random from the main survey. Allowance has been made for the degree of prematurity in each of the three premature groups. Table 4 gives the average D.Q. for children in four birth weight groups, the difference in D.Q. compared with children mature at birth, and tests of significance for this difference. It will be seen that the average D.Q. rises steadily with increasing birth weight, and in each case the difference is significant. However, it is only in the smallest weight group that a substantial difference in D.Q. is found. The prematurely born children, as a whole, tend to come from an inferior socio-economic level than those in the mature group, and there is no doubt that the intelligence of the parents in the latter group tends to be higher and the home environment more favourable. This, by itself, may account for the

TABLE 4
AVERAGE D.Q. LEVELS IN PREMATURE AND MATURE CHILDREN

	Birth Weight (lb. oz.)			
	5·9 and Over	4·9 to 5·8	3·1 to 4·8	3 and Under
Average D.Q.	106	99	95	81
Difference from mature group		7	11	2·5
t		2·36	2·98	7·84
p		0·025	0·01	0·001

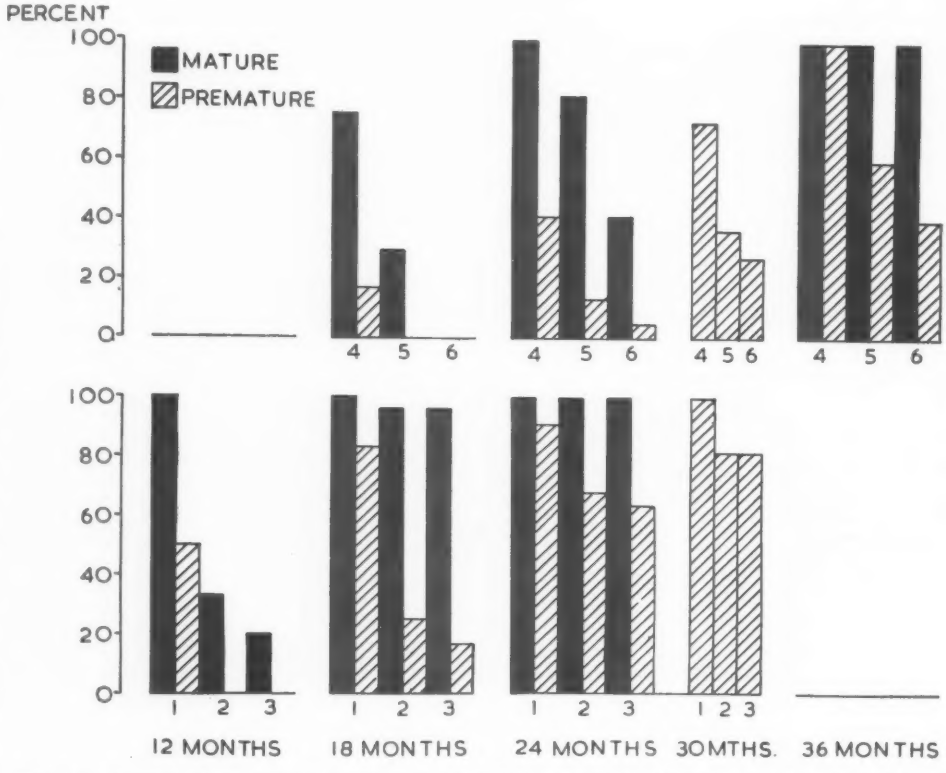

FIG. 7.—Milestones of development in premature and mature children: (1) sitting, (2) standing, (3) walking, (4) single words, (5) phrases, (6) sentences.

small differences found in D.Q. level between the larger premature children and the mature children. However, in the smallest weight group the difference is so great that it seems probable that the low D.Q. scores are directly connected with the low birth weight.

The ages at which certain milestones were passed in locomotion and speech development in the first three years have been compared in those who were 3 lb. or under at birth and those over 5½ lb. and the results are shown in Fig. 7.

The lower section of the figure shows the number of children, expressed as a percentage, at any given age who were able to (1) sit unsupported for 10 minutes or longer; (2) stand unsupported for 30 seconds or longer; (3) walk alone across a room.

The upper section shows the percentage who (4) had five or six definite words, apart from Mamma and Dadda; (5) had many single words and several two- or three-word phrases; (6) were speaking in broken sentences.

The maturely born children were not examined at 30 months. It will be seen that for locomotor activities the premature group had nearly reached the 18-month mature level by the age of 30 months, and, in speech, at 3 years they were still rather behind the mature 2-year-old level.

It is not possible to say at this stage whether there is likely to be any substantial improvement as the children get older. Out of 21 children under 3 years of age seen at regular intervals, 13 have remained at approximately the same D.Q. level (a change up or down of 8 points or less), six have definitely improved and two have deteriorated.

An attempt has been made to correlate conditions at birth and during the first few weeks of life with later mental development. In 59 cases, full records were available. In 15 cases, the baby's condition at birth was very poor, respiration was established with difficulty and cyanotic or cerebral attacks occurred during the next two weeks. Ten of these babies later showed definite mental retardation. In 36 cases, the babies caused little anxiety either at the birth or during their stay in hospital. Of these, 15 later appeared to be definitely retarded. In general one may say that it appears very difficult to judge from immediate post-natal findings what the ultimate prognosis will be.

Mental Development in School Age Children

Five school age children are attending the Royal Blind School, Edinburgh. In supplying an estimate of intelligence, the Headmaster stressed the difficulty of obtaining accurate I.Q. scores in the presence of emotional difficulties.

Age		I.Q.
Yr.	Mth.	
5	10	80 approximately
6	2	80 to 95
6	11	80 approximately
6	2	Testing impossible owing to considerable degree of emotional disturbance, but both appear retarded
6	9	

Thirteen children attending the ordinary primary schools were given intelligence tests. Terman and Merrill L or M scale tests were used except in the case of one Polish boy with a poor grasp of the English language, who was also given the Wechsler intelligence scale for children.

The estimated I.Q.s of these children and assessments of educational attainments are as follows:

Age			
Yr.	Mth.	I.Q.	Educational Attainment
5	5	109	Satisfactory start with formal work
6	1	77	Not ready for formal work
6	5	84	Below average, especially in number work
6	6	87	Below average, especially in number work. To be kept back one year. Twin (3 lb. 6 oz.) is in class for age
6	10	Wechsler Verbal 81 Performance 101	Successfully overcoming handicaps of poor health (spastic) and language difficulties
6	11	82	Severely retarded but has defective vision and hearing
7	4	89	In class for age
7	6	80	Severely retarded. Has been kept back one year
8	3	91	Is in class for age
8	3	83	Is in class for age
8	3	85	Severely retarded especially in number work. Has been kept back one year
9	2	84	Is in class for age

Three children have not been given intelligence tests. Class teachers' reports are given below:

Age		
Yr.	Mth.	Educational Attainment
6	4	Below average but making progress
7	0	Below average. Has been kept back one year. Twin (3 lb. 7 oz.) is in class for age
8	8	Below average in all subjects

Of a total of 21 children, therefore, only three are considered to be of average intelligence and the majority are very dull. However, they all entered school at the usual age and at present are considered to be of sufficient intelligence to benefit from normal primary schooling. In the pre-school group of 38 children, at least seven appear to be so grossly retarded that it seems unlikely that they will be able to begin school at 5 years, or attend normal school.

In general the school age children appear to show

less mental damage than those born in the past three years. This may be due to the fact that there is steady improvement with increasing age, but it seems more likely that with improved techniques in premature baby care damaged children are now surviving who would not have done so some years ago. This supposition is strengthened by the fact that of a total of six children with cerebral diplegia, only one is of school age, the other five being 3 years old or younger.

Illness in Early Life

The amount of illness suffered in the early years of life by the very small premature babies has been compared with that reported during the same age period for an equal number of mature babies of like sex and age.

Table 5 gives the number of children in each group who were reported as having had no illnesses, apart from head colds and minor digestive disturbances, during the previous six months. Eleven hospital admissions, for medical illness, were reported, 10 of them in the premature group. In each case, except one where the baby was admitted to hospital for failure to thrive, the diagnosis was bronchitis or pneumonia. The premature babies appeared to be particularly susceptible to lower respiratory infections. Twenty-four episodes of bronchitis or pneumonia were reported in this group compared with seven in the mature group. Frequent chesty colds during the previous six months (the mother stating that 'the doctor is never away from the door') were reported on 24 occasions in the premature group compared with six in the mature group. The figures for other illnesses are approximately equal in the two groups, except for specific infections which were more common amongst mature babies, particularly between 2 and 3 years, no doubt due to the fact that fewer of these children were firstborn, and also that in general they were allowed out to play and mixed with other children at an earlier age.

TABLE 5

MORBIDITY IN FIRST THREE YEARS IN PREMATURE AND MATURE CHILDREN

Age	No.	No Illnesses		Percentage	
		Premature	Mature	Premature	Mature
Birth to 6 months	36	20	29	56	81
6 to 12 months ..	31	12	24	39	78
12 to 18 months ..	26	14	16	54	62
18 to 24 months ..	20	11	16	55	80
24 to 36 months ..	9	3	3	33	33

In the premature group there were two cases of spastic diplegia, one of spastic paraplegia and two of spastic hemiplegia. One child had a considerable degree of deafness, and one suffered from epilepsy. Out of a total of 12 boys, three had unilateral or bilateral inguinal hernia.

Out of a total of 29 children between the ages of 3 and 9 years, about whom a reliable history could be obtained, 12 were reported as having had frequent chesty colds, bronchitis and pneumonia. One boy, aged 5 years, improved as he grew older, but in the other 11 cases the predisposition to lower respiratory infections had persisted since infancy. One school age boy suffered from spastic diplegia.

Visual Defects

A high proportion of the very small, premature babies were later found to have a visual defect. Out of 43 children between the ages of $2\frac{1}{2}$ years and 9 years, 21 (49%) were found to have some visual defect, as shown in Table 6. Twenty of the total were of school age and all of them had been seen by the school ophthalmologist. Twenty-three were under school age and had not been seen by an ophthalmologist, except in cases of obvious defect. In the school age group, 13 were found to have some abnormality, *i.e.*, 65%. In the pre-school group, 35% had an obvious defect. It therefore seems probable that some of the pre-school children may be found to have some minor defect of vision when they go up for routine examination on entry into school.

TABLE 6

VISUAL DEFECTS IN 43 CHILDREN AGED $2\frac{1}{2}$ TO 9 YEARS

Retrolental fibroplasia			5
Multiple congenital abnormalities			1
Myopia			11
Low myopia		2	
Moderate myopia		3	
High myopia		6	
Associated squint	7		
No associated squint	4		
Hypermetropia with squint			1
Convergent squint with negligible refractive error			3
Total			21

The commonest disorder found was myopia of varying degree. Eleven children were found with this condition, six of them with a considerable degree involving fundal changes. Five children had retrolental fibroplasia with very little useful vision. Of the school age group, five were attending the Royal Blind School.

Emotional Disorders

All the mothers were questioned as to the behaviour of the child: how he reacted to other

children and adults, whether there had been any particular problems associated with toilet training, sleeping or feeding habits, and in particular whether the child had been more difficult to handle than his siblings.

Children under the age of 3 years are not included in these results as minor behaviour problems are so common between the ages of 18 months and 3 years as to be considered a part of normal development.

Out of a total of 42 children between the ages of 3 and 9 years, 14 mothers stated that the child had been easy to handle and that there had not been any but minor problems of behaviour. In 28 cases (66·7%), there were, or had been, problems of sufficient degree to be considered abnormal in the particular age group concerned. In 14 cases (33·3%), the emotional disorders could be considered of quite a severe degree. In 17 cases, the child was described as being excessively timid and shy and very dependent on the mother. Characteristically the mother would state that the child was reluctant to go out to play, could never be left with a neighbour, refused to attend Sunday school with older brothers and sisters, and, in the case of school-age children, took a long time to settle down at school. One boy, who lived close to his school, ran away home at play time every day during his first two years at school. Developmental testing with these children was very difficult, cooperation was poor, the child clinging to mother and crying, or remaining obstinately silent. Physical examination and measuring were often resisted vigorously.

Eleven children were described as being highly strung, excitable and nervous, with many fears. Toilet problems and persistent bedwetting after the age of 5 years were reported in six cases. One boy, who attended the ordinary public school, was totally incontinent until the age of 7. Nine children were said to indulge in wild temper tantrums. Head banging, induced vomiting and breath holding were reported in the 3-5 age-group. Two school-age children would throw themselves on the floor, kicking and screaming when thwarted. Sleeping problems and night terrors were described in six cases. One boy of 6 years wakes nearly every night screaming and has to be taken into the parents' bed. This had been going on for several years.

The Headmaster of the Royal Blind School stated that the cases of retrolental fibroplasia attending the school were generally more difficult to handle, and less mature emotionally than other blind children of normal birth weight.

Thirty of the children examined had older or younger siblings. In 11 cases the mother stated that the premature baby had been no more difficult to handle than her other children. In 19 cases (63%) the child has always been more difficult than siblings of normal birth weight.

In four cases the child was one of twins, the other child being over 3 lb. at birth.

Case 1. These twins are aged 7 (twin I, birth weight, 2 lb. 14 oz., twin II, birth weight, 3 lb. 7 oz.), and both children have always been easy to handle. Neither has exhibited any marked behaviour problems. However, the mother says that the smaller twin has always been 'mothered' and protected by the larger and is very dependent on her.

Case 2. These twins are 3 years old. (twin I, birth weight, 2 lb. 12 oz., twin II, birth weight, 5 lb. 2 oz.). The mother has little control over either child. They both exhibit marked temper tantrums and are generally difficult to handle. However, the larger twin is much more independent. The smaller twin is said to be more excitable and highly strung and very dependent on the mother.

Case 3. These twins are 3½ years old (twin I, birth weight, 2 lb. 15 oz., twin II, birth weight, 4 lb. 2 oz.). The larger twin was friendly and cooperative and had always been much easier to handle. The smaller twin showed marked sleeping and feeding problems, was much more dependent on the mother, and was excessively timid and shy. She still indulged in temper tantrums 12 months after her brother had grown out of this phase.

Case 4. The twins are 7 years old (twin I, birth weight, 2 lb. 15 oz., twin II, birth weight, 3 lb. 6 oz.). The mother described the smaller twin as having always been highly strung, nervous and very excitable, in contrast to the larger twin who had never given any anxiety.

It is difficult to know whether the emotional immaturity of many of these children is a direct consequence of their low birth weight or whether it results from over-protection by the parents, and a transference of maternal anxiety to the child. It is possible that the deprivation of normal maternal care during the first few months of life may have some bearing on this problem. Bowlby (1953) suggests that the bad effects of separation from the mother may be evident from the age of a few weeks.

It seems likely that in at least one-third of these cases the emotional instability and immaturity may be as great a handicap to the child in later life as physical inferiority and mental slowness.

Discussion

A study of the growth and development of these 69 children with a very low birth weight suggests that the prognosis for the very small, premature

infant is considerably worse than that reported by other workers. American writers suggest that at least 50% will be physically normal and rather more will be average in mentality. Corner (1952) reports on 70 surviving babies weighing less than 3 lb. 4 oz. at birth and states that 53 (76%) were absolutely normal physically and mentally. However, in few of these investigations are details given of physical measurements, mental testing, or any indication as to what standards of normality are employed. It is possible that more detailed examination would have led to different conclusions.

When each case in this study was considered separately, it was found that at least two-thirds of the total were definitely handicapped as a result of their small birth weight. Moreover, if cases of retrolental fibroplasia are excluded, it was found that as many children in the 1-3-year-old group were severely handicapped as those in the school age group. It appears likely that as the survival rate in this low birth weight group improves an increasing number of damaged children will survive.

Summary

The results can be summarized as follows:

Physical Growth. The majority were considerably below average in both weight and height. Out of 64 children, only five had reached the expected weight for their age, and six out of 53 had reached the expected height. The retardation in weight was the most marked, the children being underweight for their height as well as generally small.

Mental Development. In a group of 38 pre-school children, only 14 were considered to have a development quotient of 90 or over. In the school age group of 21 children, three were considered to be of average intelligence.

Morbidity. Children in this low birth weight group appeared to be particularly susceptible to lower respiratory infections. In children of 3 years and under, the incidence was four times as high as that in a matched control group of maturely born children.

Physical Handicaps. Out of 31 children between the ages of 1 and 3 years, five were found to suffer from cerebral diplegia. One further case was found in the school-age group.

One-half of the children had a visual defect, and in one-third this could be considered a definite handicap.

Emotional Disorders. Behaviour problems were reported in two-thirds of the cases, and in one third the emotional disorder could be considered of quite a severe degree.

At least two-thirds of infants in the low birth weight group sustained physical, mental or emotional handicap in later infancy and childhood. This figure is considerably in excess of previous estimates and, moreover, about twice as many under-3-year-old children were severely handicapped as in those of school age. It is suggested that as the survival rate of very small premature infants improves an increasing proportion of damaged infants will survive.

I am indebted to the following, who supplied the data for the section on mental development in the school age group: Dr. W. N. Boog Watson, Chief Executive School Medical Officer, Edinburgh; Miss A. T. Paterson, Principal Educational Psychologist, Edinburgh; Dr. J. Riddell, Medical Officer of Health, Midlothian and Peeblesshire; Dr. C. B. Ross, County Medical Officer of Health, West Lothian; Dr. H. D. Wilson, County Medical Officer, East Lothian; Dr. A. Allan, Medical Officer of Health, Berwickshire; Mr. C. H. W. G. Anderson, Headmaster of the Royal Blind School, Edinburgh, and Dr. G. S. Dhillon, School Ophthalmologist, who provided ophthalmic reports on school age children. I would also like to thank Professor R. W. B. Ellis for his assistance and encouragement throughout.

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THE PROGNOSIS OF BRONCHIECTASIS IN CHILDHOOD*

BY

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In England Ogilvie (1941), Field (1949) and Conway (1952) have collected cases of childhood bronchiectasis over the long term and on the large scale needed for worthwhile information. The gloomy prognostication, based on old clinical and necropsy studies, that the bronchiectatic child will not grow up or will be a burden to himself and his neighbours, is not generally true. Since 1926—that is, during 20 to 30 years of active bronchography—the diagnosis has depended on an *x*-ray appearance of dilatation in more or less of the bronchial tree. On this basis it seems now established that: (1) dilatation once present always persists, except where tubular widening is confined to lobes or segments temporarily collapsed (atelectatic reversible bronchiectasis); (2) under natural conditions the distribution of the affected areas does not alter; and (3) the clinical picture changes little and the tendency is for any change to be for the better even without surgery and without chemotherapy.

In 1944, I (Franklin, 1944) reviewed 24 personal cases of bronchiectasis, observed for periods of four and a half to 13 years, and found 15 of them completely well and free from symptoms, while four were assessed as invalids, and five were classed as delicate according to criteria described below. The *x*-ray evidence of bronchiectasis had remained constant in distribution throughout the period of observation in all but one of the cases. This boy had the severest form of bronchiectasis clinically, with the added complications of steatorrhoea, an anaemia of pernicious type, and for a short period signs of subacute combined degeneration of the cord. Despite all this and the fact that the bronchiectatic areas spread he is, at the age of 23, well grown, normal and healthy and has been free from respiratory symptoms for six years. With a further follow-up it is possible to take from this whole group 19 cases with an interval from the onset of symptoms of between 13 and 26 years, and one with an interval of 34 years. In all but two the period of observation exceeds 10 years. Of the 20 patients (Table 1), one died aged 20 years of cerebral abscess (before 1944) and three are invalids with severe cough and much purulent sputum. Three, despite large amounts of sputum, are usually well and in light employment. Two are well except for occasional attacks of pneumonia. The remaining 11 patients are completely well and free from symptoms. Of those graded well in 1944, in only one case has there been deterioration, with the copious production of sputum, following an A1 assessment and entry into the British Army. In all the others any change has been for the better.

In 1945 the Meath School of Recovery (for the care of bronchiectatic children aged 5 to 8 years) was opened by the Invalid Children's Aid Association of London through the stimulus of Dr. Elaine Field. I had to assess cases for admission and to see them over their six to 18 months' stay, and have recently reviewed them all or seen clinical reports or *x*-ray series from their own paediatricians or chest surgeons. Out of 191 admissions between January, 1946, and December, 1952, eight were non-proven cases, 12 were inadequately followed up and the remaining 171 are included in the survey. Children were admitted because too ill to attend day school from home; for convalescence and schooling before, between and sometimes after lung resection; for social reasons, for example, to allow an unmarried mother to work; or when home conditions were considered too bad for a child with chronic respiratory disease.

As the school provided physiotherapy and postural drainage the amount of sputum and cough was stressed at first, but it soon became evident that some ill and undernourished children had little sputum or cough, while others with a great deal of both were extremely well and full of energy. The cases were then grouped (Table 2) as invalid (38 cases), delicate (70 cases) and well (63 cases). The label *invalid* is applied where sputum is of inexhaustible amount or there is failure to

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TABLE 1

LONG-TERM ASSESSMENT OF 20 PREVIOUSLY REPORTED CASES OF BRONCHIECTASIS (FRANKLIN, 1944)

Assessment in 1944 and Case No.	Age at Follow-up (years)	Observation Period (years)	Age at Onset (years)	Duration of Symptoms (years)	Final Assessment
Invalid .. 3	20	10	4	16	Died aged 20 years
4	20	12	9/12	19	Delicate (1944)
6	18	12	4	14	Invalid (1944)
7	25	19	3/12	25	Well
11	19	15	2	17	Invalid
Delicate .. 6	18	6	1	17	Delicate (1944)
12	23	16	Birth	23	Invalid. (Left lower lobectomy at age 19)
19	25	21	6/12	25	Age 23: empyema. Age 25: light employment. (Gross sputum)
21	25	22	2	23	Delicate. Light employment. (Gross sputum)
Absolutely well 1	34	22	3/52	34	Well
2	18	9	8/12	18	Well (1944)
5	27	17	6/12	26	Well
9	23	12	4	19	Well
10	23	20	Birth	23	Well, but treated for duodenal ulcer
13	20	14	4	16	Well
15	26	19	6	20	Well
17	22	10	8	14	Well
18	15	11	2	13	Well
20	22	15	4	18	Well
24	22	19	3	19	Well. (A1 in Army. Gross sputum)

thrive or crippling bronchitis or asthma; a child is labelled *well* not only in the absence of symptoms but also, if growth and energy are normal, when there are minimal amounts of sputum easily cleared, or periodic bronchitis, asthma or fever. The middle group, called *delicate*, have sputum that can be cleared though with difficulty, are capable of some exertion, but tire easily and cannot be described as well. The dividing lines, though not exact, are drawn by one observer.

At the final assessment with the same grouping standards, 15 are invalid, 23 delicate, three have died and 130 out of 171 are well, the follow-up time (not the duration of disease) being three to 10 years. Those classed as well are well grown and lead a full, normal life at school or in employment; 91 are completely free from symptoms, but 39 have traces of sputum, occasional cough, bronchitis or febrile attacks, without notable interference with the conduct of life. Table 2 shows that of 38 originally classed as invalid 14 are well, while of 63 originally well three have become invalid. All three have been operated on, none with complete removal of all affected areas. Three patients have died, one from chloramphenicol treatment, one from cor pulmonale at 16 years after a temporary improvement following partial surgery. The third died as the result of anaesthesia for bronchography, and a fourth might have joined her but for a timely tracheotomy. In these deaths treatment or diagnosis is deeply involved. This might at least discourage the routine annual stocktaking bronchogram.

Tradition demands a statement about finger-clubbing, which in this series was a measure of the degree and activity of infection, disappearing with symptomatic improvement or recovery. The more lobes involved—'lobes' meaning lobe or segment of a lobe—(Table 3) the worse the condition, and much purulent sputum is more likely with saccular than with tubular dilatation. Collapse is commonly reported in radiographs of bronchiectasis, but except in the 'well' group there is usually dilatation of

TABLE 2

FINAL ASSESSMENT OF CASES GROUPED ACCORDING TO ORIGINAL ASSESSMENT

Assessment at Entry to Meath School	Total Cases	Final Assessment			
		Invalid	Delicate	Dead	Well
Invalid	38	10	12	2	14
Delicate ..	70	2	6	1	61
Well	63	3	5	0	55
Total ..	171	15	23	3	130

TABLE 3

NUMBER OF LOBES AND TYPE OF DILATATION IN EACH GROUP

No. of Lobes	Assessment at Entry			Total (171 cases)
	Invalid (38 cases)	Delicate (70 cases)	Well (63 cases)	
1	3	19	18	40
2	6	17	13	36
3	10	18	20	48
4	15	14	11	40
5	4	2	1	7
Saccular ..	22	18	8	48
Fusiform ..	2	3	2	7
Tubular ..	14	49	53	116

bronchi outside the collapsed area and a permanent airless shadow may well be cast by a shrunken fibrous lobe.

Evidence of upper respiratory tract disease was present in all but 30 of the cases (Table 4). In another 46 cases there was either a history of removal of tonsils and adenoids or a simple nasal discharge, or both. In at least half of the invalid and the delicate cases upper respiratory symptoms contributed to the clinical picture. The relation between upper respiratory infection in general, and sinus disease in particular, and bronchiectasis is open to dispute, and the problem of which causes which may be solved by regarding bronchiectasis as sometimes part of a disease of the entire respiratory tract, improvement in one part leading to improvement in the other, but improvement in both being needed for the relief of symptoms. Lobectomy alone has accomplished little in the presence of chronic bronchitis and sinusitis, but if sinus or aural disease can be cleared up the lung condition usually improves.

TABLE 4
UPPER RESPIRATORY INFECTION

	Assessment at Entry		
	Invalid (38 cases)	Delicate (70 cases)	Well (63 cases)
Nasal discharge	19	28	23
Sinus infection	19	28	23
Sinus operation ..	13	21	17
Aural discharge	6	9	13
Aural operation	1	3	3
Removal of tonsils and adenoids	16	45	41
Nasal discharge or removal of tonsils and adenoids alone or in combination ..	8	25	13
No upper respiratory disease	12	10	8

The early onset of symptoms is striking, these starting before the age of 2 years in 99 of 171 cases (Table 5). Some prognostic importance for this is suggested by the fact that this onset of symptoms before the age of 2 years occurred in 13 of 15 judged invalid at the final assessment, in five of the seven cases where all five lobes are involved in 19 of the 20 with severe nutritional disturbance and in 20 of the 22 cases of saccular dilatation in those classed as invalid at entry. That this cannot be blamed on the character of the onset of symptoms is shown in Table 6, which compares the mode of onset in all cases and those beginning under the age of 2 years. There is no appreciable difference in the percentage distribution. Could the greater severity of the disease when the onset is early be due to infection of the lung at a particular stage of its growth?

TABLE 5
AGE AT ONSET OF RESPIRATORY SYMPTOMS

Age at Onset (years)	No. of Cases		Age at Onset (years)	No. of Cases	
Under 1 ..	61	99	5–6	7	
1–2 ..	38		6–7	2	15
2–3 ..	30		7–8	2	
3–4 ..	18	57	8–9	3	
4–5 ..	9		Uncertain	1	

TABLE 6
CHARACTER OF ONSET

Type of Onset	Total (171 cases)	Per cent. of All Cases (100)	Onset Under 2 Years (99 cases)
From birth	6*	3·5	6
No acute illness ..	56	32·8	35
Pneumonia	51	29·8	31
Whooping-cough ..	32	18·6	16
Measles	19	11·1	9
Other	7	4·2	2

* Plus one case of neonatal pneumonia.
NOTE: Only one case presented as tuberculosis, but four more were probably cases of primary infection, and tuberculosis was present in at least 12 cases, all arising after the age of 2 years.

Although elaborate classifications of bronchiectasis have been suggested in the past, we are inclined now to think and speak of and to treat bronchiectasis as an entity. Accuracy in prognosis might be helped by classifying cases into aetiological groups and clinical types. Certainly the progressive and serious lung lesions in cases of pancreatic fibrosis should be excluded. At the other end of the scale atelectatic unilobar disease should also be excluded unless time proves that the changes persist following expansion of the lung. Empyema complicating pneumonia at onset was found in seven cases, and all these benefited from surgery. The role of tuberculosis is more difficult to determine. The tuberculin state is known only in 50 cases, and was positive in 15 and negative in 35. Only one case presented as tuberculosis, but review suggests that it was important in 11 others, four with primary lesions and seven with collapse or bronchostenosis secondary to enlarged lymph nodes. The particularly suggestive clinical features are an onset after the age of 2 years, involvement localized to one lobe or one lung, temporary finger-clubbing (in two only while there was cough and sputum), a high incidence of 'collapse' and a low one of upper respiratory disease. All cases but one are now in the 'perfectly well' group. Surgery is usually unnecessary for the relief of cough and sputum, and its use depends on the general policy adopted for the surgical treatment of childhood intrathoracic tuberculosis.

Prognosis has been considered in relation to the major clinical types of the disease. In the classical case there is much purulent sputum, often abnormal physical signs in the chest and finger-clubbing. The patient at rest punctuates time with the typical cough, a deep and effortless rattle, while exertion, emotion or changes of posture cause periodic productive paroxysms. There is a small group with some clinical symptoms and signs suggesting the disease, but with bronchitis and asthma as the prominent features, and a still smaller group with recurrent fever and occasional respiratory signs and symptoms. Haemoptysis as the sole evidence of bronchiectasis must be rare in children. Table 7

TABLE 7
ASSESSMENT AT ENTRY AND TYPE OF CLINICAL PICTURE

Assessment at Entry	Total Cases	Classical: Cough and Purulent Sputum	Bronchitic and Asthmatic	Recurrent Febrile Attacks
Invalid ..	38	36	2	0
Delicate ..	70	52	14	4
Well ..	63	41	11	11*
Total ..	171	129	27	15

* Including one case of inhaled foreign body and one of tuberculosis.

correlates the assessment at entry with these clinical types, and shows the high incidence of classical cases in the invalid group in contrast with the low incidence of invalids in either bronchitic or febrile cases. The large number of patients, 40, who are classed as well in the group labelled classical needs comment. These children had a classical history and many had the clinical evidence of bronchiectasis at the preliminary examination and even on arrival at the home. The picture though clear was always mild and was short-lived, so that within a few days or weeks of arrival neither cough nor expectoration could be induced by exercise, tipping or tapping.

This review covers the most active period in the surgical attack on children with bronchiectasis. A total of 71 cases were operated on, including 60 of the 129 classical cases, 26 of which had complete excision of all affected areas and 34 excision of part only. Some of these operations, as judged by the clinical rather than the radiological picture, seem to have been cosmetic, and some to have been carried out to allay the unjustified fear of spread of disease or of deterioration of health. Where there was complete resection of all areas known to be affected 17 of 26 patients are well, but nine retain symptoms of cough and sputum. Of the 34 with partial surgical treatment, 12 are well despite the continued presence of bronchiectatic areas. In one-half of the non-surgical classical cases the patients are well. This group contains milder cases, but also 14 patients with large amounts of sputum who escaped surgery because of the widespread disease. Of the 28 bronchitic cases, seven had complete, three partial and 18 no operation. Few if any would have been treated surgically now. One case of recurrent fever out of 15 had complete surgery with improvement. The presentation of figures is difficult and may be misleading, since numbers are small and anything approaching matched controls is impossible. The series lacks consistency because many physicians and surgeons using different criteria were in charge of the cases. The results may at least be claimed to show that surgery is not the complete therapeutic answer. The risk of post-operative pulmonary collapse and consequent spread of bronchiectasis is less than was feared at first, but extensive surgery may increase dyspnoea on exertion and diminish mixing efficiency in the lungs.

The prognosis of any chronic or disabling disease cannot be made on a purely anatomical basis. Sixteen patients (almost one in 10) were of sufficiently low intelligence to require special educational methods, and such cases do badly. The doctor's advice, as well as his methods of diagnosis and treatment, may affect the situation in unintended ways. The only unmanageable boy had been away from home continuously from the age of 10 months to 5 years because of respiratory illness. Twenty-nine other patients were separated from home in early life for long periods on medical advice, though only four of these were led by behaviour disturbance to the Child Guidance Clinic. In six cases great fear of the disease had been induced in parents and children by the doctor's terrible prognosis or by his arguments in favour of surgery. Repeated bronchograms, radiographs and surgical operations take a toll of morale. The record is held by one boy who had 56 *x*-ray exposures in two years. Thirty-five homes were judged physically unsatisfactory, and 10 children from slums undoubtedly improved after rehousing in a new area. Although in three cases operative treatment was considered wisest because of relapse on return to bad housing conditions, in the whole series the physical environment affected the results surprisingly little.

To sketch briefly the course of the commonest, the classical case, the onset is early in life following pneumonia, perhaps complicating whooping-cough or measles or both in succession. The cough, the sputum, with clubbing, cyanosis, abnormal physical

signs in the chest and chest deformities, are severe from the outset and continue for five or six years punctuated by recurrent pneumonia. In the lucky case the symptoms gradually improve and at 12 or 13 years of age the child is in comparatively good health except for some productive cough, increasing with any respiratory infection. Later in adolescence the symptoms disappear. In the unlucky case with severe and extensive bilateral saccular disease, chronic pneumonitis leads to permanent invalidism, possibly with cor pulmonale. Such cases are usually too extensive for surgery, while the use of antibiotics, despite a reduction in sputum and a disappearance of bacterial infection, leaves the secretion of copious mucus and the abnormal physical and radiological signs and causes little improvement in the patient's symptoms. By contrast, the mild case dries up with a course of the appropriate antibiotic and may remain free from symptoms for many months or years.

The results in the series reviewed seem quite good. The bad cases, the 15 who remain invalids, are bad indeed, and to prevent such cases seems the only solution. May I suggest that the prognosis is worst with an onset under 2 years of age, that the respiratory tract is often involved as a whole, the bronchial dilatation being only a part of what is wrong; that the extent of the disease is unlikely to change, so that repeated bronchography with its slight though definite risk is unnecessary; that selection of cases for operation requires prolonged observation and deep knowledge of the individual case; and that in assessing prognosis before deciding on treatment the natural history of bronchiectasis be remembered and the whole child and his environment be considered, so that treatment is avoided that might be more harmful than the disease itself.

I acknowledge gratefully the help of Miss Gosling, the Matron at the Meath Home at the relevant period, the staff of the Invalid Children's Aid Association, and the many colleagues in the fields of paediatrics, thoracic surgery and radiology, who have so unselfishly produced clinical records and radiographs and have sanctioned the follow-up visits of their patients. I would also thank the children and their parents for their cooperation, including much travelling.

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A CONSIDERATION OF COLOSTRUM AND MILK AS SOURCES OF ANTIBODIES WHICH MAY BE TRANSFERRED TO THE NEWBORN BABY

BY

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The fact that antibodies can be conveyed to a newborn animal by colostrum was first shown by Ehrlich (1892). In his experiments artificial antibodies to abrin and ricin were induced in mice; after exchange of litters of immunized and non-immunized animals, the litters suckled from immunized mothers had acquired some measure of protection to abrin and ricin. Although the antibodies of colostrum are known to be absorbed unaltered by the newborn calf and lamb (Mason, Dalling and Gordon, 1930), there has been no clear evidence that such absorption occurs in human beings. If it does occur it is of less significance and is harder to detect because the baby, unlike a calf or lamb, is endowed before birth with maternal antibodies which it receives transplacentally. Thus the maternal serum, and therefore the infant's serum, will contain antibodies of the same specificity as the colostrum. When the baby is fed by its mother, absorption from the colostrum can be recognized only by an increase of the antibodies already in the baby's serum.

The question of absorption, even in small quantities, of unaltered antibodies is of importance, although the effects of depriving the child of colostrum or breast milk are not dramatic as in ungulates. We need to know what qualities or substances in breast milk contribute to the baby's defences and make the incidence of infection lower than among the bottle-fed. The lower incidence of gastro-enteritis among breast-fed babies (Douglas, 1950) could be explained by postulating less exposure to infection, but Douglas also found a significant protection against measles conferred by suckling. This protection showed a correlation with the length of lactation and lasted longer. The finding suggested that over a long period of breast feeding small amounts of globulin or antibody are absorbed or derived from the milk, or alternatively that breast milk influences the baby's hormonal or other control of its own antibodies. The widespread belief in the benefit of breast milk for premature babies conforms with the idea of antibody transfer, since the serum globulin is low in premature infants (Rimington and Bickford, 1946). If the protection which milk confers depends on the absorption of unaltered antibodies, heat treatment of breast milk should be avoided so far as is possible. If, on the other hand, the globulins of colostrum and milk are broken down in digestion and yet contribute to the baby's specific immunity, they do so presumably by providing the material for the rebuilt globulins, and heat treatment might be expected to have little or no effect. The possibility of absorption of unaltered antibodies is also of more direct and obvious importance in deciding whether an Rh-negative mother with Rh antibodies in her serum, colostrum and milk should feed her Rh-positive infant from the breast, or whether this would increase the severity of the haemolytic disease of the newborn from which it was already suffering.

In the investigation described here the anti-A and anti-B content of maternal serum, colostrum and milk, and of infant's serum taken at birth and at 3 and 10 days post partum, was determined. This was done in order to find the range of titration values and whether there was any correlation between them, for instance, whether a high titre of agglutinins in the maternal serum is associated with a high titre of the same agglutinins in the colostrum and milk, and whether the agglutinins of colostrum and milk pass unaltered through the digestive tract of the infant and appear in its serum. It was hoped in this way to measure the contribution of maternal antibodies which might be expected in completely normal physiological circumstances when any other effects such as the antitryptic effect of colostrum would be in full play. The question also

arose whether the agglutinins might cause or prolong haemolytic disease of the newborn.

In the second part of the study a number of Rh-negative babies were bottle-fed with fluids containing anti-D antibodies and their sera examined at intervals for the appearance of these antibodies.

Serological Methods

The ABO grouping and Rh typing of maternal and cord samples was by the standard tube technique. The ABO grouping included tests on the cells and serum of each individual.

Titration of Antibodies. The anti-A and anti-B agglutinins were titrated in the maternal serum taken at the time of delivery, in the colostrum on the third day and in the milk on the tenth day. In the infant the anti-A and anti-B agglutinins of the cord serum were titrated, also those of serum obtained by heel prick on the third and tenth days after birth.

The method used for titration of antibodies in serum was essentially as described by Taylor and Ikin (1939). Doubling dilutions of test serum were made in saline with a Pasteur pipette graduated to deliver a constant volume (about 0·03 ml.). To each of the dilutions an equal volume of a 2% suspension of appropriate red cells was added, the cells being always from the same donors and freshly drawn each day. The titrations were made in duplicate and allowed to stand at room temperature for two to three hours, after which the contents of the tubes were examined for agglutination both macroscopically and microscopically. The presence of evenly distributed clumps of three or more cells was accepted as evidence of agglutination. The titre of a serum sample was expressed as the reciprocal of the highest dilution of serum causing agglutination.

The maternal colostrum and milk were titrated in exactly the same way as the serum. It was, however, found necessary to centrifuge these fluids rapidly for five minutes so that the cream could be removed from the surface and discarded. Colostrum and milk also agglutinated Group O cells but the titration value was low; however, a titration against Group O cells was included for each sample (see also Hirszfeld and Lille-Szyszkowicz, 1949).

Complete or saline-agglutinating Rh antibodies were titrated in a similar way, but were incubated at 37° C. instead of at room temperature. Owing to the fragile nature of the agglutinates, great care was taken in handling the contents of each tube when reading the tests. The standard red cells used were of the genotypes R_1R_1 (CDeCDe) and R_2r (cDEcde), together with rr (cdecde) as a negative control.

For the titration of incomplete or albumin-agglutinating Rh antibodies a slightly modified technique was used. The serial dilutions of the serum being tested were made in AB serum instead of saline and an equal volume of a 2% suspension of standard red cells in bovine albumin was added to each tube. The same precautions were taken in reading the tests.

Detection of Rh Antibodies. Four techniques were employed for the detection of anti-Rh (anti-D) antibodies in the baby's serum.

(*a*) SALINE TECHNIQUE. Equal volumes of the serum to be tested and a 2% suspension of standard cells were incubated for two hours and then the red cells were examined microscopically for agglutination, the Rh genotypes of the cells used being the same as those for the titration of saline agglutinins.

(*b*) ALBUMIN TECHNIQUE. Equal volumes of serum and a 2% suspension of red cells made in 30% bovine albumin were incubated for two hours and the tests read in the same manner as for the saline technique. For this test the standard cells used were of genotypes R_1R_2 (CDecDE) and rr (cdecde).

(*c*) INDIRECT COOMBS TECHNIQUE. Equal volumes of serum to be tested and a 5% suspension of standard red cells were incubated for two hours at 37° C. The red cells were then carefully washed three times in saline and a drop of anti-human-globulin serum was mixed with them on a slide. The slide was then gently rocked and the smear examined for agglutination, if necessary microscopically. The results were not recorded as negative until the slides had been under observation for five minutes. The anti-globulin reagent was controlled against known sensitized cells with each batch of tests. Each serum examined was tested against three D-positive and two D-negative samples of standard cells.

(*d*) TRYPSIN TECHNIQUE. A stock solution was made by dissolving 0·1 g. of crystalline trypsin (Armour) in 10 ml. $\frac{N}{20}$ HCl. Each day before use the trypsin solution was diluted 1 in 10 with 0·1 M phosphate buffer at *p*H 7·7. This buffered enzyme was added to twice-washed cells of the appropriated Rh type in the proportion of four parts of solution to one part of packed red cells. (The red cells used for trypsin testing are freshly bled into 3·7% sodium citrate solution, separated by centrifugation and washed twice with 0·85% saline.) After adding buffered trypsin solution the red cells were incubated at 37° C. for 30 minutes, then washed twice in warm saline at 37° C. Before adding the trypsin-treated cells to the test sera a 2-4% suspension of the cells was made in warm saline. Equal volumes of test serum and trypsinized red cells were incubated for approximately one hour at 37° C. and the tests read for agglutination. In the case of trypsin tests it is not advisable to handle the cell sediments too gently or false positive results may be obtained. The same standard cells were used for the test as for the indirect Coombs test.

Part I: Titres of Anti-A and Anti-B Isoagglutinins in Colostrum and Milk and Infants' Sera

Samples were taken from 97 mothers and their babies. Of the mothers, 52 belonged to Group O, 39 to Group A, four to Group B and two to Group AB. The anti-A and anti-B agglutinins were titrated in the maternal serum taken at the time of delivery, in the colostrum on the third day post

partum and in the milk on the tenth day. The baby's serum was tested for the presence of anti-A and anti-B agglutinins in the cord blood at birth and at the third and tenth days of life. Cases in which the baby was small were not included, nor were those in which breast feeding was unsuccessful.

Results. The titres of anti-A and anti-B agglutinins in the maternal serum ranged from 16 to 1,000; in the milk, from 1 to 1,000; and in the colostrum, from 2 to 64,000. In most cases the concentration of agglutinins was higher in colostrum than in milk.

The titres of anti-A and anti-B agglutinins in the infant's serum were low, ranging from 0 to 16, and the majority of them were less than 8. The relationship between titres of agglutinins in colostrum and in milk and those in maternal serum and colostrum, and the change of titre in the infant's serum and colostrum, are shown in Figs. 1-3. (In these diagrams the titre is expressed in units of the number of serial dilutions and not in the actual dilution.) These relationships are all in respect of the anti-B agglutinin, because owing to the distribution of ABO blood groups there are many more cases in which the anti-B agglutinin is compatible with the infant's red cells.

A true picture of the state of affairs with regard to agglutinins that are incompatible with the infant's red cells cannot be obtained owing to absorption of these agglutinins by the infant's tissues and body fluids.

Discussion. Figs. 1 and 2 show that there is some correlation between titres of agglutinins in colostrum and milk and between those of maternal serum and colostrum, the tendency being for women with high serum titres to possess the highest colostrum titres, and also, as might be expected, high colostrum titres were followed by higher titres of antibody in the milk.

Evidence of an effect of colostrum titre on that of the infant's serum was sought by plotting the colostrum titre against the change in titre in the infant's serum between birth and the tenth day (Fig. 3). No significant correlation was found, nor was there any correlation when the titres of milk were similarly plotted.

The range of titre of the agglutinin in colostrum in this group of cases was between 2 and 8,000. Assuming that the effect of dilution would be similar if it were absorbed unchanged, it was thought that some difference in titre in the sera of babies after the ingestion of colostrum with this range of titre variation might be detectable. With complete absorption the dilution in the baby's intravascular fluids would be of the order of one in six for each ounce taken. By the tenth day a baby fully fed from the breast may have received between one-half and two-thirds of its birth weight in colostrum and milk. Even if most of the secretion were milk a substantial absorption of agglutinins might reasonably be expected to be reflected in the infant's serum. The

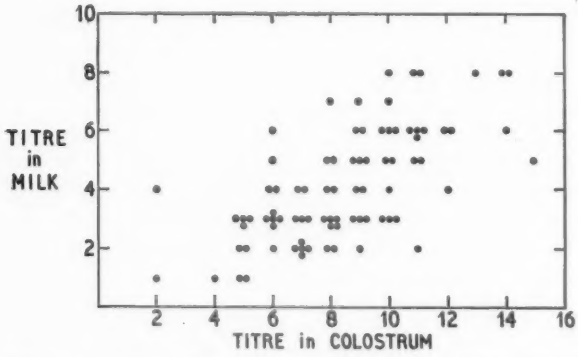

FIG. 1.—Relationship between titres of agglutinins in colostrum and milk.

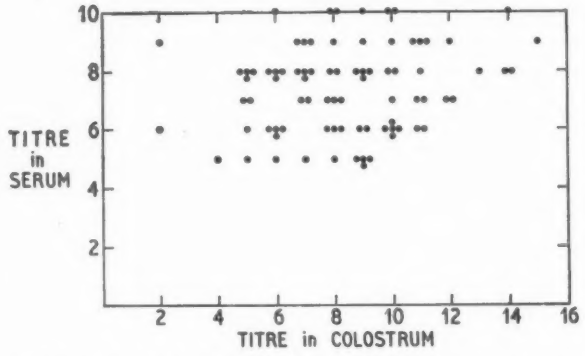

FIG. 2.—Relationship between titres of agglutinins in maternal serum and colostrum.

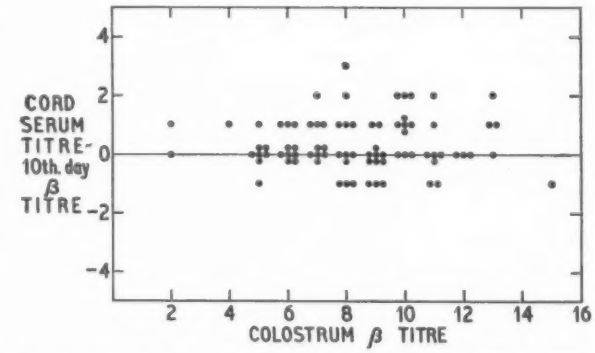

FIG. 3.—Showing effect of colostrum titre on that of infant's serum.

range of titre in the colostrum and milk was so great that it is unlikely that variations in the amount taken would have obscured evidence of absorption if it had occurred in more than trace amounts.

It is of interest to note that in the cases in which the infant was taking large quantities of incompatible agglutinin with the colostrum and milk, for example, Group A babies of Group O mothers in some of whom the colostrum titres were 512-4,000, no sign of jaundice or anaemia was observed in the baby.

The fact that a few infants' sera showed agglutinin titres above 8 seems to indicate that occasionally saline agglutinins as opposed to incomplete antibodies are able to cross the placental barrier and enter the foetal circulation. In the opinion of some workers only incomplete antibodies are capable of this.

The above study of anti-A and anti-B content of maternal serum, milk and colostrum are an early one and a measure of incomplete antibodies was made. Very recently some evidence in a few cases had been obtained for the transfer of incomplete anti-A from mother to milk and from milk to infant (Munk-Anderson, Aagaard and Dyggve, 1957).

Part II: Inhibition of Rh Antibodies by Newborn Babies

Method. Either milk or serum containing Rh antibodies of high titre was given by mouth to normal babies. The Rh type was determined from the cord blood at birth, and feeding of the material was started as soon as possible afterwards. The antibody containing material had been collected from suitable donors and stored at −18° C. until required. It was gently warmed to a suitable temperature for the baby, and the residue from each feed was saved and titrated to confirm that the heat had not altered the titration value. The infant's serum was obtained by heel puncture and in every case samples were taken during feeding and approximately daily for two or three days afterwards.

In all, 21 babies were fed with either serum or milk containing Rh antibodies. The first 11 of these were investigated before the introduction of the very sensitive trypsin technique for the detection of incomplete antibodies, and the last 10 cases were investigated with this technique as well as the indirect Coombs technique.

With one exception Rh-negative babies were selected to avoid possible injury to the baby and also to eliminate the risk of antibodies becoming attached specifically to tissue cells and thus not being detectable in the circulation.

Milk containing Rh antibodies was given to one Rh-negative and one Rh-positive baby, and serum containing Rh-antibodies of both complete and incomplete types was fed to the remaining 19. High-titre fluids were deliberately selected in order to obtain the maximum chance of detecting antibody in the infant's circulation if present. The first dose of the material was given as early as possible in life; two babies even received it within two hours of birth. This timing was chosen to test the possibility that absorption in human beings resembles that in ungulates: absorption is almost quantitative in calves and lambs during the first 24 hours, but virtually ceases after 48 hours. The serum was either fed

TABLE

Case No.	Rhesus Group	Age of Baby when Antibody Received	Material Taken and Volume (ml.)	Titre and Type of Antibody	Maximum Effective Volume (litres)	Birth Weight (kg.)	Fraction of Dose Estimated Detectable in Intravascular Plasma
1	Rh+	4–9 days	Milk 278	64	26	3·71	1 in 40
2	Rh−	12 hrs.–5 days	Serum 340	64	16	3·97	1 in 80
3	Rh−	12 hrs.–2 days	Serum 119	16	2	2·79	1 in 13
4	Rh−	12 hrs.–3 days	Serum 153	32	6	3·09	1 in 40
5	Rh−	2–5 days	Serum 26	1,000	27	3·69	1 in 140
6	Rh−	18 hrs.–4 days	Milk 810	8	3	3·00	1 in 20
7	Rh−	11–19 hrs.	Serum 17	1,000; saline	17	4·17	1 in 82
8	Rh−	12–24 hrs.	Serum 25	1,000; saline	25	3·32	1 in 150
9	Rh−	12–24 hrs.	Serum 25	1,000; saline	25	3·00	1 in 166
10	Rh−	2–10 hrs.	Serum 17	2,000; saline	34	4·03	1 in 170
11	Rh−	2–4 hrs.	Serum 18	2,000; saline	36	3·74	1 in 194
12	Rh−	13–38 hrs.	Serum 47	1,000; saline	47	3·44	1 in 273
13	Rh−	15–35 hrs.	Serum 18	1,000; albumin	18	3·64	1 in 100
14	Rh−	17–36 hrs.	Serum 22	512; albumin	10	3·34	1 in 61
15	Rh−	15–36 hrs.	Serum 22	1,000; albumin	22	3·05	1 in 44
16	Rh−	10–29 hrs.	Serum 20	512; albumin	8	3·05	1 in 52
17	Rh−	27–50 hrs.	Serum 17	512; albumin	8	3·76	1 in 43
18	Rh−	53–85 hrs.	Serum 21	256; saline	5	3·10	1 in 32
19	Rh−	36–41 hrs.	Serum 12	512; albumin	6	3·08	1 in 39
20	Rh−	3–40 hrs.	Serum 23	256; saline	5	3·60	1 in 28
21	Rh−	8–33 hrs.	Serum 16	512; albumin	8	3·40	1 in 47

Cases 12–21 received the serum together with colostrum.

mixed with measured amounts of fresh colostrum, or given immediately after the feed from the breast in eight cases in order that the antitryptic effect of colostrum or any other unsuspected factor which might assist in antibody absorption might play its physiological rôle.

Results. The accompanying Table gives the volume and titre of the material and the time it was given, together with the birth weight of the baby. Some measure is needed to show what proportion of the antibody would have to be absorbed in order to be detected, although an estimation of this kind can be only approximate. From this it will be assumed that the material, if absorbed unaltered, dispersed round the body, and when obtained in serum from a heel prick would agglutinate cells at a final dilution corresponding to that in the original serum. This leaves no allowance for any 'carry-over' effect in the original titration. If the number of millilitres of each dose of material is multiplied by the highest dilution at which agglutination is obtained, the sum of all the products for all the doses given to one baby amounts to a volume to which the entire dose might be diluted and still be detectable. If this hypothetical effective volume is compared with the baby's intravascular fluid volume a proportion is obtained which shows very roughly how much of the dose would have to be absorbed to be detectable. These findings are also summarized in the Table, which gives the hypothetical effective volume and its relation to the baby's intravascular fluid. In no case were Rh antibodies detected in the serum after the infant had been fed with milk or serum containing these antibodies in high titre. In the first 11 cases tests were made by saline and indirect Coombs techniques, using red cells from individuals homozygous for antigen D as well as Rh-negative cells as a negative control. In the last 10 cases tests by the trypsin technique were also included, since in some instances it has been shown that this technique will reveal the presence of antibodies when other techniques fail.

Discussion. The volume of milk or serum fed to the babies was necessarily less than the amount of milk a baby obtains by suckling, but the titre of the material was very much higher than the titres commonly found in the breast secretion of women with antibodies. In the course of the search for colostrum and milk with Rh antibodies of high titre many samples were examined. The milk eventually obtained and used for feeding was of exceptionally high titre.

If one may assume that antibodies of high titre, when diluted, are comparable to weak ones, the amounts of antibodies received by the babies were within the range of doses commonly transferred by suckling in the first days of life. It is, however, possible that the absorption of antibodies from colostrum might be different from absorption from serum since, for instance, colostrum contains trypsin inhibitors (Laskowski and Laskowski, 1951).

Antibodies, if absorbed, would be detectable only if the rate of their destruction or removal were relatively slow. The rate of disappearance of other passive immune bodies has been found to extend over weeks rather than days (Barr, Glenny and Randall, 1949). This slow rate was confirmed in the present investigation by studying the fall in titre in babies' sera. Two babies, the unaffected children of mothers with Rh antibodies from previous sensitization, received Rh antibodies transplacentally. These remained detectable for two weeks. Two were given antibody intravenously and the rate of disappearance of the antibody in these two cases is given in Fig. 4. It is concluded that the negative

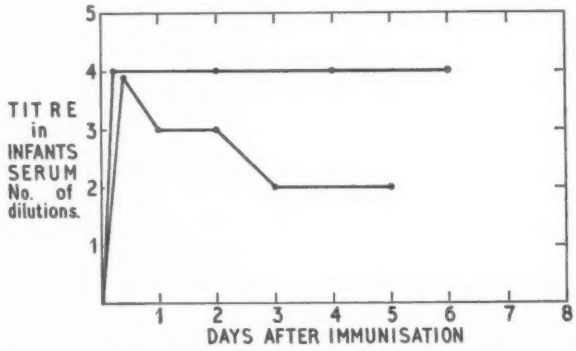

FIG. 4.—Showing rate of disappearance of antibody given intravenously to two babies.

result of the tests for absorbed agglutinins was not attributable to quick removal of the antibody or to ill timing of the sampling of the infant's serum.

Cathie (1947) also found no evidence of absorption of unaltered antibodies. His material was given to Rh-positive individuals, one man and several children, the youngest apparently being 1 week old. He concluded that there was no justification for weaning infants with haemolytic disease on account of the presence of Rh antibodies in the breast milk. Since his subjects were Rh positive there was a likelihood that if partial absorption occurred, the antibodies might become attached to tissues without becoming detectable in the serum. The dosage given in the present investigation and the fact that the subjects were Rh negative are believed to have ensured that if even only a small

proportion of the antibody given were absorbed it would have been detected. The fact that no absorbed antibody was found in the infant's serum is not regarded as conclusive evidence that Rh-positive babies of mothers with Rh antibodies may be fed from the breast during the first days of life. It seems undesirable to give a baby, whether mildly or severely affected with haemolytic disease, more of the one substance from which it is suffering. The mechanism, whether it is intestinal juice, gut wall or liver, which prevents free absorption is unknown; nor is it known whether the mechanism is injured in affected babies. Since affected babies are nearly always the offspring of multiparae, the maintenance of lactation without putting the baby to the breast is usually practicable for the seven or eight days until the agglutinin titre of the milk has fallen. During this time expressed milk may be boiled and given to the baby, and direct feeding started on the eighth day.

The slow elimination of passive immune bodies and the range of dosage used in this investigation still leave a possibility that a baby could slowly accumulate rather than lose antibodies although no absorption has been detected. The protection afforded by breast milk against measles (Douglas) already mentioned hints that this is so. It is therefore recommended that a baby born with cells sensitized by Rh agglutinins should be fed from the breast after eight days and fed with heated expressed breast milk until then. Moreover, since we have not been able to demonstrate the transfer of antibodies from milk and colostrum to the infant, there is no reason to suppose that by heating the breast milk the baby is being deprived of other kinds of antibody which are beneficial.

Summary

Part I. Samples of serum, colostrum and milk from 97 mothers and their infants were tested for their anti-A and anti-B content.

The titres of anti-A and anti-B agglutinins in the maternal serum ranged from 16 to 1,000, in the milk from 1 to 1,000, in the colostrum from 2 to 64,000 and in the infant's serum from 0 to 16. Some correlation was noted between titres of agglutinins in colostrum and milk and between those of maternal serum and colostrum. No correlation was established between titres of colostrum or milk and the infants' serum.

Part II. Serum and milk containing Rh antibodies were given to one Rh-positive and 20 Rh-negative infants in the first days of life.

The infants' sera were tested for Rh antibodies by saline and indirect Coombs techniques in the first 11 cases, and by saline, indirect Coombs and trypsin techniques in the last 10 cases. No Rh antibodies were detected.

The material given would have been detectable after dilution in the baby's intravascular fluid if approximately one in 150 parts was absorbed unaltered.

The material was given to some babies within 24 hours of birth. Absorption comparable to that which occurs in ungulates immediately after birth was not found.

The sensitivity of the methods used does not preclude absorption of traces of unaltered antibodies by babies already affected by Rh antibodies. Expression and heat treatment of breast milk during the first eight days is recommended where the baby's cells are sensitized.

Our thanks are due to Dr. J. F. Loutit, Dr. R. A. Zeitlin and Miss Doreen Daley for their help and cooperation in this work, most of which was carried out while we were employed by the Medical Research Council.

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THE SERUM PROTEINS AT 6 MONTHS OF AGE IN INFANTS FED ON HUMAN OR COW'S MILK OR ON BOTH

BY

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The finding by Douglas (1950) that breast-fed babies possess an immunity to measles which bottle-fed babies do not, and the fact that the administration of γ globulin can protect a baby from the infection, suggested that babies receiving human milk might have a greater serum γ globulin content than those giving cow's milk from a bottle. In a serological investigation of neonatal antibodies Boorman, Dodd and Gunther (1958) could detect no increase in the baby's circulating Rh antibodies as a result of feeding high-titre serum; nor could they find any effect on serum isoagglutinins from the consumption of colostrum and milk of varying titres of anti-A and anti-B agglutinins which the babies received from their mothers. It seemed possible, however, that γ globulins were more readily absorbed or rebuilt, even though they might lose their particular immunological specificity, from human rather than bovine globulins taken by mouth. The absorption of serum proteins of the animal's own species and not of others has been suggested by Dent and Schilling (1948) from their work on dogs. Although the total quantity of γ globulin needed to alter a baby's susceptibility to measles is small, it seemed worth while to see whether a detectable difference in the serum proteins was produced over a period of months by different methods of feeding.

Present Investigation

In the investigation here reported comparison was made of the serum from babies who were known to have received only one kind of milk, human or bovine, from birth or a mixture of both. By 6 months of age they had, however, all received other foods in small quantities. The total protein in the serum at 6 months of age was estimated by the density method of Linderstrøm-Lang and Lanz (1938) as modified by Lowry and Hunter (1945). The serum was subjected to electrophoresis on a paper strip (Flynn and de Mayo, 1951) and the components were estimated by a scanner and direct transmission of light (Crook, Harris and Warren, 1952).

Results

The sera from the three groups of infants, receiving (*a*) breast milk, (*b*) cow's milk or (*c*) a mixture of human and cow's milk, showed no significant differences in their content of total protein and none in the content of the components of albumin and of α_1, α_2, β and γ globulin (see Table).

It is concluded that no differences in the serum protein levels resulting from feeding the infants with human or cow's milk could be detected in the samples by micro-electrophoretic analysis.

Our best thanks go to Professor F. L. Warren and to Dr. N. R. Butler for their help.

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TABLE

SERUM PROTEINS OF BABIES AT 6 MONTHS FED WITH HUMAN OR COW'S MILK OR A MIXTURE OF BOTH

Feeding	No. of Cases	Mean Birth Weight (g.)	Total Protein (g./100 ml.)		Albumin %		α_1 Globulin %		α_2 Globulin %		β Globulin %		γ Globulin %	
					Rel.	Absol.	Rel.	Absol.	Rel.	Absol.	Rel.	Absol.	Rel.	Absol.
Breast	11	3,400	Mean	6·42	64·56	4·16	4·61	0·293	10·12	0·64	12·87	0·82	7·64	0·48
			S.D.	0·55	3·69	0·55	0·95	0·048	2·43	0·14	1·89	0·13	2·59	0·127
Bottle	6	3,515	Mean	6·37	65·1	4·15	5·42	0·41	10·01	0·64	11·75	0·72	7·74	0·49
			S.D.	0·57	2·38	0·34	0·69	0·073	1·28	0·097	2·24	0·09	2·52	0·19
Mixed	11	3,285	Mean	6·16	62·5	3·79	5·58	0·34	10·91	0·67	13·25	0·81	7·80	0·48
			S.D.	0·47	4·24	0·91	1·32	0·073	1·66	0·117	1·64	0·085	1·92	0·12

THE DIETARY TREATMENT OF PHENYLKETONURIA

BY

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Phenylketonuria is an inborn error of the metabolism of phenylalanine associated almost invariably with grave mental deficiency, and often with epilepsy resembling petit mal. It was suggested that the mental deficiency was due to an intoxication by phenylalanine or one of its metabolites and might be relieved by feeding a diet low in phenylalanine (Woolf and Vulliamy, 1951). An economically practicable form of such a diet, based on a charcoal-treated casein acid hydrolysate, was devised by one of us (L.I.W.) and first fed to a phenylketonuric child by Bickel, Gerrard and Hickmans (1953).* They reported a dramatic improvement in mentality in their patient and Woolf, Griffiths and Moncrieff (1955), using objective psychometric methods, found a marked improvement in three other cases. Since then there have been a number of reports of the successful application of the dietary treatment of phenylketonuria (*e.g.*, Armstrong and Tyler, 1955; Braude, 1956; Horner and Streamer, 1956; Blainey and Gulliford, 1956), and it is evidently being widely adopted. We are reporting here our experiences both with the original three patients (now followed for a further 32 months) and with a further seven phenylketonuric children who have been treated on the diet for periods varying from 11 to 34 months. One of these has been treated from the age of a few weeks for over two years, and has remained in the normal range of intelligence. Another, treated from the age of 4 months, has not shown the further deterioration in intelligence which would be expected if untreated. The rest have all improved in intelligence rating; in two of the four cases with fits these ceased soon after the children were placed on the diet, and the E.E.G. became nearly normal (*cf.* Wolf, 1956).

Of the children who have been or are being treated with the diet at this hospital, all but eight are reported here. Of these eight, one lives at a considerable distance, while the other seven have been treated for too short a time to enable any conclusions to be drawn.

* It was Dr. Bickel who undertook the laborious task of preparing the charcoal-treated casein hydrolysate, now commercially available, and who courageously first gave it to a phenylketonuric patient.

Clinical Summaries

Case 1. This child, a sibling of Case 9, was born in February, 1955, weighing 6 lb. 3 oz. (her twin sister, born first, weighed 7 lb. 10 oz. at birth). Urine obtained on the seventeenth day of life contained phenylpyruvic acid and both twins were admitted at the age of 3 weeks. Phenylpyruvic acid could not be detected in the urine of the twin sister and paper chromatography showed that her urinary phenylalanine concentration was normal. Dr. Cedric Carter kindly saw them and tests showed conclusively that they are dizygous. The blood group of Case 1 was O, NN, CD (probable genotype R_1R_1) and of the normal twin O, NN, CDc (probable genotype R_1r). Both children appeared normal physically, and clinically about identical in behaviour. Intelligence tests were carried out on both twins and will be discussed later. The affected twin was weaned from the breast and a special synthetic 'milk', low in phenylalanine was started (see page 39), and she was quickly worked up to an intake of 50 calories per lb. per day. She lost a little weight and the intake was increased at first to 60 calories per lb. and then to 70 calories as she appeared to be hungry. The weight increased rather slowly and the amount of cow's milk added to the diet was several times increased, each increase accelerating the weight gain. She became anaemic in appearance, the haemoglobin fell and a blood transfusion was given. Clinically, she did not appear quite as bright as her twin sister but intelligence testing gave a very satisfactory result, showing her to be average at the age of 15 weeks, with a 'general quotient'* (G.Q.) of 99. She was re-admitted with a bad 'cold' at the age of 5 months having continued on her special 'milk' as an out-patient. At the age of 6 months, she weighed 14 lb. 10 oz. and was doing very well physically and mentally. The urine remained free from phenylpyruvic acid. She became difficult over feeds and was re-admitted for weaning on to a more solid diet but this proved an impossible task, and weaning was delayed for a further few months. She was successfully weaned on to solids at 15 months and is now getting a mixed diet like that of her older sister (Case 9). Her mother did not think

* The G.Q. is derived from a scale (Griffiths, 1954) suitable for testing very young children of low mental age (see page 34).

her progress quite so good as her twin sister's but intelligence tests were satisfactory, the child's G.Q. having reached a 'plateau' of about 88. An E.E.G. was performed on June 13, 1956, and was within normal limits as far as could be ascertained on a short record with the eyes open.

For several months she had very little hair on her head. When it finally grew it was golden, exactly the same colour as her normal twin sister's and unlike the grey-blonde characteristic of phenylketonuria. (The family was fair-haired, see Case 9.)

Case 2. This girl, born on October 9, 1951, was under the care of Dr. P. R. Evans. She originally attended at the age of just over 1 year for muscular weakness and failure to thrive. There had been a few attacks which were possibly 'fits'. The urine was not examined for phenylpyruvic acid at this time. Her retardation was not great and progress continued. She walked at just under 2 years. At this time phenylketonuria was diagnosed but no treatment was instituted. A year later in view of success with the diet in other cases she was admitted, and a phenylalanine-free diet was started in September, 1954. She was at this time a blue-eyed blonde with an I.Q. of 71. There have been no fits since the age of 2 years (on no medicaments). An E.E.G. in 1954, before the condition was first treated, was normal. Her physical development is normal. She had been a contact with a patient with active pulmonary tuberculosis, and her Mantoux reaction became positive in November, 1954, but the child has shown no evidence of the disease. The phenylalanine-free diet has been maintained since the autumn of 1954, though with occasional mild lapses. In the autumn of 1956, her I.Q. having reached the level of 92, she started school, being nearly 5 years old. Her teacher has said, 'She is a normal child, no different from the others.'

Case 3. This child was born on February 17, 1951, and the following is a summary of the previous clinical account (Woolf *et al.*, 1955).

One older brother is a proved phenylketonuric. Case 3 was late in sitting up, standing and walking. She had no illnesses and no fits. Phenylketonuria was discovered at the age of 2 years 7 months and dietary treatment was begun in October, 1953. An E.E.G. was normal and her G.Q. was 42. Her very pale hair became dark under treatment.

CONTINUATION OF HISTORY. She was re-admitted for assessment in January, 1954, and appeared to be progressing. She was more active than before. Phenylpyruvic acid was absent from the urine. Similar results were found when admitted in April, 1954, and again in July, 1954. She was admitted to Tadworth Branch Hospital in September, 1954, for three weeks while her parents had a holiday. Her urine remained free from phenylpyruvic acid. She had a slight gastro-intestinal upset in October, 1954. The clinical impression was one of continuing improvement. In April, 1956, it was noted that her parents were inclined to be careless and phenylpyruvic acid was found in the urine on one occasion. Her I.Q., which had been rising steadily, levelled off at 57, and then slipped back to 52 at this time. The dietary errors were corrected and her I.Q. has risen to 65 (January, 1957). She is now aged 6 years, and has lessons several times a week from a visiting Surrey County Council teacher.

Case 4. This boy was born on February 20, 1951. The following is a summary of a previous clinical account (Woolf *et al.*, 1955).

The milestones were passed late. Fits occurred at 6 months of age. Phenylketonuria was discovered at the age of 2 years and 8 months. An E.E.G. in October, 1953, was abnormal, and diagnostic of epilepsy. The special diet was started in October, 1953. By January, 1954, an E.E.G. showed none of the previously reported abnormal features. A subsequent E.E.G. showed no specific epileptic activity. His ash-blonde hair became darker. Difficulties over the diet at home caused him to be admitted to the branch hospital at Tadworth. During the period September, 1953, to October, 1954, his G.Q. rose from 20 to 31 while he was on the diet.

CONTINUATION OF HISTORY. He was admitted to The Hospital for Sick Children and its country branch from July 28, 1954, to August 3, 1955, mainly because of home difficulties. He had acute appendicitis in January, 1955, but made an uneventful post-operative recovery. Walking improved and he had no fits. The general impression of his last few months at Tadworth in 1955 was that there was no noticeable improvement in physical and mental achievements. He was seen in the Out-patient Department in September, 1955, at the age of 4½ years. He weighed 17·8 kg. He could walk unaided, though unsteadily, but could not talk and was still doubly incontinent. He had had no fits. After careful consideration of his physical state and the results of intelligence testing, it was decided to discontinue the special diet, especially in view of recurrent difficulties at home. An E.E.G. in June, 1955, showed in a sleep record evidence of some epileptic activity, with high-voltage spikes and slow components, but it was not strictly comparable with previous records which were taken with the eyes open. Only slight 'fits' have recurred, confined to his waking on occasional mornings three times or so each week. Another E.E.G. in June, 1956, did not show any epileptic outbursts but there were frequent artefacts which makes the record unreliable. Clinically he was still having occasional fits when wakening out of sleep but these were not so severe as previously. He is on no sedative drugs or any special diet now (June, 1956). His mother thinks he is continuing to improve slowly in all he does and is not going back. He actually continues at a low level of G.Q. 20, the same as before treatment was started.

Case 5. This child born on December 13, 1948, was described by Woolf *et al.*, 1955, and the following is a summary:

An older brother is a proved phenylketonuric ament, and there is one normal sister. At the age of 3 months it was thought that she did not recognize her parents.

She could sit by 1 year. At the age of 15 months she began to have fits. An E.E.G. showed spike-and-wave discharges. Her I.Q. was estimated to be about 40 at the age of 20 months. Phenylpyruvic acid was found in the urine. Fits, resembling petit mal, continued but ceased abruptly in December, 1953, on aloxidone and amphetamine sulphate. She could stand with support at 3 years. An E.E.G. in April, 1954, showed slow spike-and-wave complexes during sleep. Dietary treatment began at the age of 5 years 4 months in May, 1954. There was a curious attack of major epilepsy after 25 days of diet with unconsciousness and cardiac failure. Her hair darkened very markedly during treatment.

CONTINUATION OF HISTORY. She was admitted to Tadworth Branch Hospital to give her parents a holiday. The cardiac failure had completely resolved. No fits occurred (she was still on sedatives), but she was still very retarded. She was seen in the Out-patient Department from time to time and also admitted for re-assessment in September, 1954. An E.E.G. in September, 1954, showed very frequent bursts of irregular spike-and-wave complexes in the sleeping record, but no epileptic activity when awake. Later she developed some severe fits. She began to crawl about the end of the year. It was eventually decided to stop the special diet gradually, starting on April 21, 1955, as very little progress was being made. Several severe fits occurred and she was admitted in 'status epilepticus' on May 8, 1955. The fits were controlled with intramuscular paraldehyde followed by aloxidone, and she remained free from fits up to November, 1956, when last seen, continuing treatment by aloxidone. On that date she was still unable to walk alone or to swallow solids. Her mother thinks she has deteriorated and is losing skills she once possessed.

Case 6. This child, born on March 10, 1955, is the second of two children. He was brought to hospital under the care of Dr. P. R. Evans at the age of 16 months with an older backward brother who was found to have phenylketonuria. This child's urine was therefore tested and he was found to have phenylketonuria. He had been thought to be normal up to 8 months of age although he did not hold up his head until 6 months. When first seen he could not crawl or walk and had only been sitting up for two months. He was a fair-haired, blue-eyed child. There was no history of fits but a doubtful episode resembling petit mal occurred while he was an in-patient. The E.E.G. was not abnormal except for tracings from the pre-frontal region which were perhaps abnormally flat. The G.Q. was 57 on the Griffiths scale. A low phenylalanine diet was started. He has attended the Out-patient Department regularly with clinical improvement and only minor difficulties over diet. A second E.E.G. three months after the diet was begun was normal. Clinically he was thought to show some slow improvement but speech was delayed. In January, 1957, his I.Q. was 76 (Merrill-Palmer); on the Griffiths scale his G.Q. was 68 but this was an incomplete test, since he scored the maximum on several items.

Case 7. This child, born on January 6, 1951, was brought to the Out-patient Department at the age of 2½ years because she was not walking. The patient had been slightly backward with her other milestones. Phenylpyruvic acid was discovered in the urine. The parents were uncooperative from the start, refusing to accept that the child was severely retarded. A brief attempt to start a low-phenylalanine diet was abandoned because the child was removed by the parents. The E.E.G. was within normal limits. The G.Q. on the Griffiths scale was 49 (on July 2, 1953, aged 2 years 6½ months) and, on a repeat test, again 49 (August 5). The parents came back to the Out-patient Department some months later but it was decided that lack of cooperation would preclude use of a special diet. Frequent respiratory tract infections led to a further admission at the age of 4½ years when her tonsils were removed. The G.Q. at this time on the Griffiths scale was 35. She continued to attend erratically and physically made reasonable progress. The G.Q. in May, 1956, was 37, and she was being considered for an occupation centre despite her mother's continued opposition to acceptance of the diagnosis. The child never had any fits.

Case 8. This child, born on August 10, 1955, is a sister of a known phenylketonuric boy. When his condition was diagnosed her urine was examined, and she was found also to be passing phenylpyruvic acid. She was then 4 months of age and had been thought by her parents to be normal in her mental development, but clinically she seemed a little retarded. Her G.Q. (Griffith's scale) was 57. She was put on a low phenylalanine diet and proved difficult to feed on this diet. As with Case 1, phenylalanine tended to vanish completely from her blood and so cow's milk was given and increased several times in an effort to restore the blood phenylalanine level to normal. The serum proteins dropped to 4·56 g. per 100 ml., and the blood urea level rose to 67 mg./100 ml., but both returned to normal when phenylalanine reappeared in the blood in response to an increase in intake of cow's milk. After being stationary for over three weeks, her weight began to rise and she was eventually discharged. Her G.Q. at the age of 6 months was 64. Progress at home continued but seemed to slow up. At the age of 11 months she could sit only with assistance. An E.E.G. was normal. This child emigrated at the age of 14 months, preventing further testing, but the mother reports (January 3, 1957) that, at 16 months, the child stands alone and says a few words.

Case 9. This child is the sister of Case 1. She was born on March 9, 1953, and first attended The Hospital for Sick Children in April, 1954, at the age of 11 months for backwardness. She held up her head at 6 months, and sat alone at 1 year. Minor 'fits' began at about 20 months in which she dropped forward. At this time phenylpyruvic acid was found in the urine and she was admitted for further investigation. She was a typical

blonde, backward child with a general intelligence quotient of 24 (Griffiths scale). An E.E.G. was severely abnormal with very high voltage, slow delta activity associated with 'sharp' components. A low phenylalanine diet was started. Some initial loss of weight occurred with the diet as usual, but was later made good. Her hair, which had been almost albino, changed to a medium brown colour with a sharp line of demarcation between white and brown. She had no fits while she was in hospital, but no obvious improvement occurred in her mental state. She was discharged home to continue on the diet but re-admitted a few weeks later with an acute respiratory tract infection which yielded to routine treatment. The mother was pleased with progress and the child was crawling. In February, 1956, she was reported to be saying single words and had begun to walk. Aloxidone was being used but the 'fits' were not entirely controlled. Further intelligence testing in May, 1956, gave a G.Q. of 31, an improvement of four points since October, 1955, and of seven points over the lowest score of 24 in March and June, 1955. An E.E.G. on March 14, 1957, showed only doubtful or slight improvement over the one before treatment started, and was still severely abnormal with large irregular sharp waves, spikes, and slow waves, but with an unstable alpha rhythm. It is probable that except for a special feature in this case the special diet might well have been abandoned after about a year's trial but when it was started the mother was again pregnant and gave birth to twins. One of these was affected, with phenylpyruvic acid in the urine, and one was not. This very important pair of twins from the point of view of study merited great care for all the family.

Case 10. This boy (under the care of Dr. P. R. Evans) was born on December 23, 1952, and is an only child. He was said to be normal up to 3 months of age. Minor fits began at 5 months and he has been retarded ever since. The urine was found to contain phenylpyruvic acid at the age of 18 months. The G.Q. was 20 on the Griffiths scale. An E.E.G. showed diffuse epileptic changes. Major epilepsy developed about a month later. A low phenylalanine diet was started in July, 1954. Slight clinical improvement was noted. He was admitted for re-assessment about five months later. The E.E.G. was reported as erratically normal. (He was on phenobarbitone and the improvement could be due to this.) Fits were continuing but less frequently. He was re-admitted six months later. He was now aged 2½ years and for two months he had been standing and walking. There had been no fits for three months (phenobarbitone ½ grain at night). He had some difficulty over solid food. An E.E.G. was reported as 'mildly abnormal'. He has continued to attend as an out-patient. He had no more fits. The G.Q. in August, 1955, was 27 and in May, 1956, it was 34, indicating a very definite intellectual improvement. He has continued throughout on his low phenylalanine diet, but with numerous serious lapses, his mother being apparently unable to keep forbidden foods from him.

Case 11. This child was born on February 7, 1955, and was first seen (under the care of Dr. P. R. Evans) in March, 1956, at the age of 13 months, because his mother thought he ought to be doing more. Phenylpyruvic acid was found in the urine. There were no fits at any time. The G.Q. (Griffiths scale) was 21 in April, 1956. An E.E.G. showed diffuse abnormal bursts of sharp spike-and-wave activity, such as are often associated with the condition of phenylketonuria. A phenylalanine-free diet was begun but, through a manufacturer's error, *N*-acetyl-DL-tryptophan was fed instead of DL-tryptophan for the first eight weeks. His weight dropped over six days from 11·3 kg. to 11 kg., rose to 11·7 kg. soon after cow's milk was added to the diet, and then dropped steadily to 10·7 kg. During this time the blood phenylalanine level remained high, though phenylpyruvic acid did not reappear in the urine. When tryptophan was added to his diet, his weight began to increase at once, the blood phenylalanine level dropped to normal, and he obviously became much more cheerful. His hair remained the grey-blond colour characteristic of phenylketonuria throughout the period when he was unintentionally deprived of tryptophan; three days after adding tryptophan to his diet the new growth at the base of the hair was almost black, making a striking contrast with the rest of the hair.

His G.Q. (Griffiths scale) on November 8, 1956, was 23, and on April 18, 1957, it was 32. An E.E.G, on April 16, 1957, still showed a generalized abnormality with large amplitude, irregular sharp waves, spikes and slow waves, but there was an improvement over the E.E.G. of April 19, 1956, though the records are not strictly comparable.

Psychological Examinations

Careful psychometry was necessary if we were not to rely on subjective impressions of any improvement on dietary treatment. The test used had to be suitable for children of low mental age. A recently devised test (Griffiths, 1954), which had been standardized by one of us (R.G.) on about 600 children between the ages of 2 weeks and 2 years has been used throughout. The nature of this test provides for very detailed information by virtue of items divided into five sub-scales, each measuring a significant aspect of mental growth and development. This makes it possible to observe from time to time the progress in, *e.g.*, eye-hand coordination, or alertness to sounds. After the second year the scale merges into the Terman-Merrill which was the test used for children of mental age over 2 years, except in Case 6 where the Merrill-Palmer scale was used. The youngest infants were tested every six weeks, the intervals being gradually lengthened to three months during the second year.

The results are best shown in graphs of mental age plotted against chronological age (Figs. 1-4).

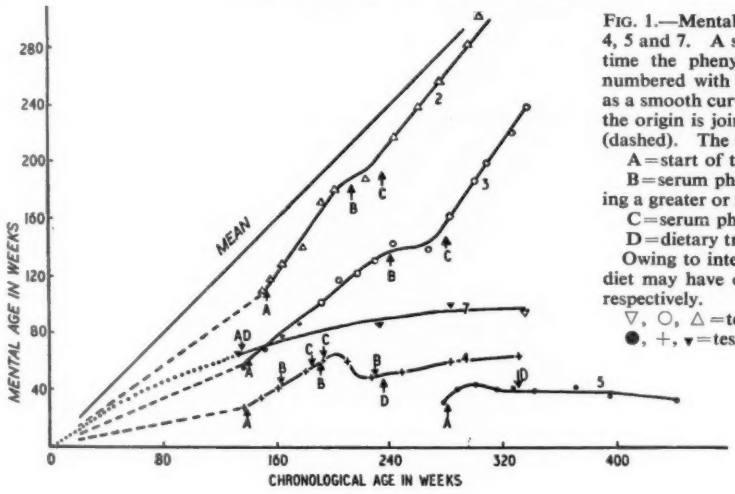

FIG. 1.—Mental age plotted against chronological age for Cases 2, 3, 4, 5 and 7. A smoothed curve is drawn through the points from the time the phenylalanine-restricted diet was started (each curve is numbered with the case no.); in Case 7 this line is continued back as a smooth curve (dotted) through the origin and in Cases 2, 3 and 4 the origin is joined to the first point in each curve by a straight line (dashed). The mean for the whole population is also shown.

A = start of the diet low in phenylalanine

B = serum phenylalanine concentration found to be raised, indicating a greater or lesser departure from the diet

C = serum phenylalanine level found to have returned to normal

D = dietary treatment terminated.

Owing to intermittent testing, the departure from or return to the diet may have occurred a little earlier than is indicated by B or C respectively.

▽, ○, △ = test results obtained on the Terman-Merrill scale.

●, +, ▾ = test results obtained on the Griffiths scale.

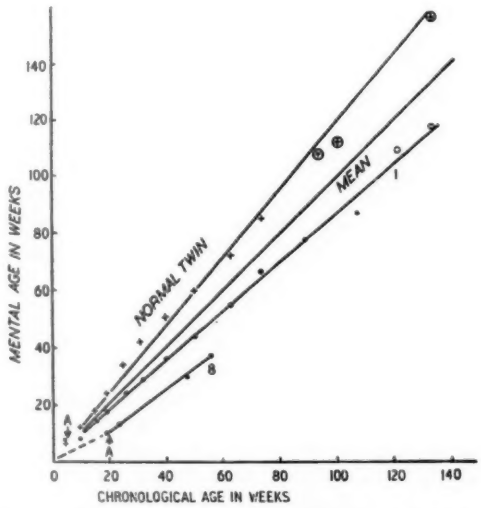

FIG. 2.—Mental age plotted against chronological age for Cases 1, 8 and the normal twin of Case 1. A as in Fig. 1.

○, ⊗ = test results obtained on the Terman-Merrill scale.

●, + = test results obtained on the Griffiths scale.

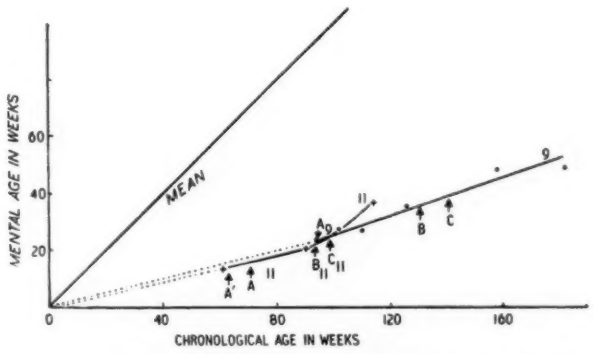

FIG. 4.—Mental age plotted against chronological age for Cases 9 and 11.

●, + = test results (Griffiths scale).

A′ = phenylalanine and tryptophan-restricted diet started.

A, B and C as in Fig. 1; where confusion might arise, the case no. is added to A, B or C as a subscript.

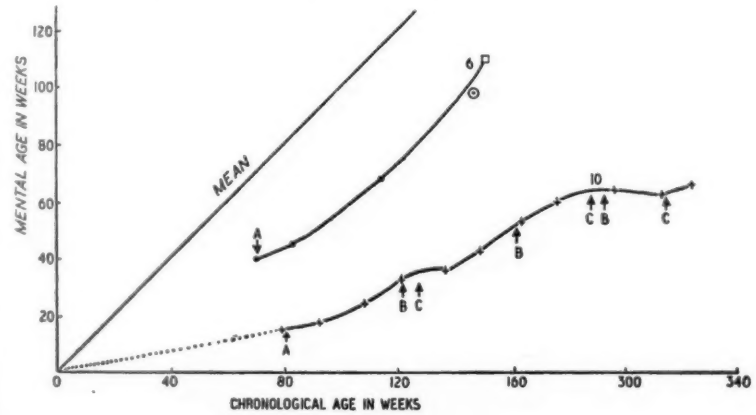

FIG. 3.—Mental age plotted against chronological age for Cases 6 and 10. A, B and C as in Fig. 1.

●, + = test results obtained on the Griffiths scale.

⊙ = result of an incomplete test on the Griffiths scale.

□ = test result on the Merrill-Palmer scale.

Fig. 5 shows the changing general intelligence quotients as time passes.*

Case 1. When first tested, at the age of 4 weeks, she was more active than her normal twin; in fact she displayed a certain hyperactivity. For example, when placed in the prone position she suddenly lifted head and shoulders well up, turned her head first to the left, then to the right, and then placed her cheek against the pillow again. Apart from this unusual physical activity, her test results were in general and in detail very like her twin sister's, and the two children actually passed and failed exactly the same test items in scales C, D and E. In subsequent tests the healthy twin continued to do well. After one very good test result (119) the G.Q. of Case 1 dropped to a fairly steady level of between 88 and 92. This has been maintained.

Case 2. Even before she went on to the diet, this child had a G.Q. of 71. She was already able to do a few tests of the Terman-Merrill scale, and this test was used for all subsequent psychological examinations. The child has made steady and quite rapid progress ever since (Fig. 1). Her speech was at first indistinct and largely babble, but this stage has long ago been left behind and her speech is now clear and fluent and developing rapidly.

Case 3. This child has been followed since October, 1953, when her G.Q. was 42. Her intelligence has improved almost continuously. At one stage (see Fig. 1, point B) there was a pause in progress; she did not do so well on tests and much of the restlessness noticed earlier had returned. It was found that the blood phenylalanine level was raised (both in this case and all the others, the blood and urinary phenylalanine levels were not known till after the intelligence testing). The diet has since then been strictly adhered to and the child has not only regained her former position but has advanced still further. When tested in November, 1956, she had reached a new level of 62.

It is highly probable that this child will prove to be educable, at least at an educationally subnormal level, but she will be continually under observation and in another year or so may be found capable of accepting education in a normal school.

Case 4. This child was described in a previous paper as Case 1 (Woolf *et al.*, 1955) as improving quite rapidly

* The raw quotients and mental ages have been given in Figs. 1-5, Differences in the standard deviations make the quotients slightly different in meaning as one passes from one type of test to another, but these do not obscure the improvement. Dr. J. A. Fraser Roberts advised us that, owing to the doubtful accuracy of the standard deviations for children of such low I.Q., it would be misleading to give the results for most of these children in terms of standard scores at the different ages.

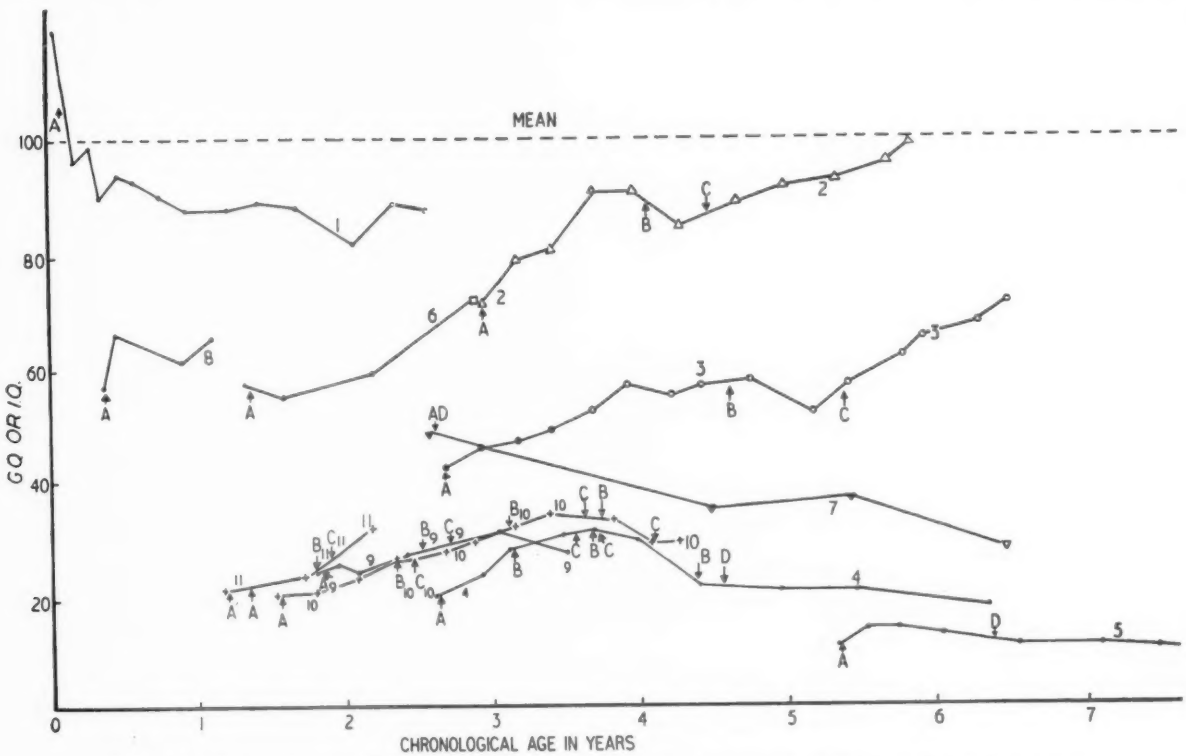

FIG. 5.—Intelligence quotient plotted against chronological age for all 11 cases, A′ A, B, C and D as in Figs. 1 to 4.
●, +, ▾=test results obtained on the Griffiths scale. ▽, ○, △=test results obtained on the Terman-Merrill scale.
□=test result obtained on the Merrill-Palmer scale.

in all directions, but particularly in regard to speech. On the diet his G.Q. rose from 20 to 30 in 10 months and his speech from Q.C.8 to Q.C.32 during the same period.

Soon after this encouraging progress, however, it was found that the child was not being kept strictly on the diet at home and phenylpyruvic acid was again found in the urine.

The results of a test on March 2, 1955, were surprising, for not only did his mental age remain exactly the same as on the last test, but every item in the test was passed or failed exactly as before. This naturally produced a drop in the G.Q. from 31 to 29. He was content to do various tests, but appeared not to recognize the examiner. He was unsteady on his feet, produced very few sounds, and the nurses reported no speech. He did not laugh or smile. He did not always fixate objects shown to him, and manipulation was vague and momentary, objects being immediately relinquished after handling. He deliberately bumped his head on the floor twice.

On June 29, 1955, he had made no progress in learning; he had in fact deteriorated, failing a few items he could previously do. He walked unsteadily, without direction, round and round in circles, and did not go after toys. He appeared not to make contact with people. Speech had regressed seriously, he had ceased to masticate, and was being fed with a spoon.

It was felt at that time that the child was suffering from a degree of emotional deprivation in this long period (10 months) away from home, sufficient to produce some signs suggestive of an early psychosis and to cause intellectual regression. As the youngest child in the home, he had previously had a good deal of attention and devoted care from his mother. The separation was working against the success of the diet. The child was apparently sent home, but the parents made little attempt to keep to the diet and he was taken off it. He has maintained his level at about G.Q. 21 to 22. He is happy, smiling and laughing, vocalizing and quite different in appearance since he was seen in the summer at Tadworth. He has re-learnt to walk upstairs, holding his mother's hand, can seat himself at table, is less vague, going towards people and after toys on the floor. He produces several clear sounds, *e.g.*, 'me-me, Babby, Dada'. His use of his hands, too, is slightly better.

Case 5. The progress of this child on the diet was slight, her G.Q. rising in the course of 12 months from 11 to 14. No further progress could be obtained. Subsequently she was taken off the diet.

Since the child came off the diet her mental age has actually dropped from 42 weeks in September, 1954, to 38 weeks in June, 1956. This negative progress rate indicates continuing deterioration and her G.Q. has dropped sharply to 10. At 7½ years of age she is intellectually and in all developmental respects like a baby of 8 months.

Case 6. This case is of interest since there was no sharp inflexion at the start of the diet, but the progress rate increased steadily (Fig. 3). During the first 10 months of treatment the G.Q. did not change significantly, but during the next eight months it rose by 17 points on the Merrill-Palmer scale. The Griffiths scale test was not completed, but even in its partial form already showed a rise of eight points. The diet was strictly adhered to throughout.

Case 9. The test results on this child demonstrate the irreversibility of some effects of the phenylketonuria if the child is too old when treatment starts. This girl was 21 months old and her G.Q. was 24; after 20 months o treatment it has only risen to 27, although it did reach a peak of 31.

For the past six months, this child has been showing behaviour which increasingly qualifies to be called psychotic. She does not make any progress in relating to people, and does not look at people. Her increasing motor skill makes more evident the poverty of the content of her thought; she staggers about aimlessly, hurting herself, biting the furniture, completely withdrawn, though her mental age is now about 12 months.

Case 10. The rise in the actual quotient of 13 points, from 20 to 33, is not in itself dramatic, but a slow and steady rise of the quotient by a few points each time is definitely significant. To know this boy, however, is to be aware of a continuous improvement, for, where he previously lay in his cot, contented enough but unable to sit or speak or play, he is now, two years later, walking and trotting about and climbing. He has a small vocabulary of words and can throw a ball and manipulate toys and bricks a little.

When seen on January 30, 1957, he was very restless and miserable and his G.Q. had dropped to 29. His urine and blood, obtained immediately after the intelligence test, contained quite a high concentration of phenylalanine, and his mother was again warned not to depart from the diet. A similar G.Q. was found on April 3, but he was much more cheerful and cooperative; his blood and urinary phenylalanine concentrations were normal.

Case 11. This child went on the diet when he was 1 year and 2 months old. Six months later the quotient had only risen two points, but the diet had not been kept strictly; six months later it had risen 11 points. This child has a persistently unhappy disposition; whenever seen in hospital, he cries continually and inconsolably; no attention his mother gives him is of any help and all activities seem equally distasteful to him. Twice the test had to be abandoned. This crying is very like that seen in a child with cerebral damage, but, on the other hand, the mother says he is not like this at home. She agrees that the home circumstances, necessitating a day nursery, are by no means ideal and may be the cause of the abnormal behaviour.

It is of interest to note that, as these children begin to progress on the diet, improvement in different kinds of activities is not uniform but tends

to accentuate what may be a characteristic profile. The first and most striking observation, patent to everybody concerned, is the increased physical activity with the accompanying progress in locomotor development. In a few weeks or months, the child may learn to sit, creep, stand and walk. He also shows improved social alertness, enjoying the contact with other people and losing some of the apathy and general mental dullness previously observed. Progress in speech and also in hand-eye coordination is frequently much slower, and manual skill may be delayed for some time. The number of cases studied in this way so far is too few for any statistical evaluation of a characteristic profile to be valid, but it appears that the child, still limited in general mental capacity, tends to concentrate on one type of activity at a time, locomotor improvement being at first most strikingly present in the majority of cases.

Feeding more protein than allowed seems, in some cases, to cause restlessness and hyperactivity. The child seems unable to concentrate on the test or to cooperate with the examiner. He seems miserable. On a number of occasions when this type of behaviour was noted, blood obtained immediately after the psychological examination was found to have a raised phenylalanine concentration. Return to the diet (as shown by subsequent chemical investigation) produced a happier, calmer and more cooperative mood.

Chemical Investigations

The diet was controlled, in each case, by repeated chemical investigation of the blood and urine. In the first three cases treated, the daily phenylalanine intake, as milk protein, was at first reduced till phenylpyruvic acid was no longer detectable in the urine, using the direct ferric chloride reaction and the more sensitive method of Berry and Woolf (1952). It was found that the concentration of phenylalanine in the blood and urine, though reduced to about one-third of its former value, was still considerably above normal when phenylpyruvic acid vanished from the urine. The amount of cow's milk fed daily was therefore controlled by keeping the phenylalanine concentration in the blood and urine at the same level as in normal children. This resulted in the milk intake being roughly halved for the first three cases (3, 4 and 5).

Paper chromatography (Woolf, 1951) was used to follow the blood and urinary amino-acids; this enabled the phenylalanine concentration to be compared with the concentrations of the other amino-acids and this balance, particularly for the blood, is more nearly related to the body's needs than is a simple determination of phenylalanine. One advantage of using this method was that any drop to below normal in blood phenylalanine level could be detected and corrected by increasing the intake of cow's milk, usually by 15 or 30 ml. per day. After each such increase or reduction, the blood phenylalanine concentration took about a fortnight to reach a new steady level.

In Case 1, the daily phenylalanine requirements rose steadily between the ages of 5 weeks and 9 months. The blood phenylalanine level was found on several occasions to be very low and there was necessarily a time lag between the subsequent increases in intake of cow's milk and retesting. The infant's growth rate was unsatisfactory at times, probably as a result of this, and on one occasion the blood urea concentration rose to 60 mg. per 100 ml., reflecting the catabolism of the unbalanced amino-acid mixture being fed. Case 8 showed similar effects of too low a phenylalanine intake.

Case 11 ceased to gain weight when placed on the diet and his blood and urinary phenylalanine concentrations remained raised, though below the point at which phenylpyruvic acid is excreted. This continued for five weeks, in spite of progressively decreasing his intake of cow's milk. His hair remained very fair and did not show the darkening at the roots that appeared so dramatically in most other phenylketonurics when placed on the diet. It was noticed that he was excreting very little tryptophan, and the various components of the diet were examined. It was found that, through an error of the manufacturer, he was being fed acetyl-DL-tryptophan instead of DL-tryptophan. When this was corrected there was a dramatic rise in his weight, his blood and urinary phenylalanine concentrations dropped sharply, and his hair turned dark at the roots within three days.

In every case, the diet did not affect the post-absorptive blood concentrations of any amino-acids except phenylalanine, methionine and α-amino-butyric acid. The blood levels of methionine and α-aminobutyric acid rose slightly when 1 g. of DL-methionine was fed daily. The urinary concentrations of methionine and tryptophan were very high; presumably the D form of both amino-acids was not appreciably reabsorbed by the kidney tubules and accounted for their high excretion. The urinary excretion of tyrosine, leucine, valine, serine and lysine was also somewhat higher than the average, though far below the levels met in diseases such as cystinosis. Probably feeding the bulk of the dietary nitrogen as a mixture of amino-acids resulted in a higher rate of absorption from the gut than when protein is fed; this would lead to an

unusually high blood amino-acid level and hence to a greater 'overflow' of amino-acids into the urine. The daily intake of casein hydrolysate was kept on the high side to correct for inefficient utilization, and a fairly high calorie intake was maintained by feeding extra carbohydrate, since dietary carbohydrate is known to affect the utilization of amino-acids (Harris and Harris, 1947; Munro and Thomson, 1953).

In every case, within a few days of starting the diet, the previously normal urinary taurine concentration fell to an extremely low level and taurine sometimes vanished from the urine. It was thought that sulphur-containing amino-acids might be deficient in the diet and so DL-methionine was added (1 g. per day for children over 1 year). This raised the urinary taurine excretion very slightly in a few cases, but had no effect at all in most, even though the urinary cystine excretion rose markedly in all cases. L-cystine was fed to Case 1 to see whether the slow absorption of this amino-acid from the gut was necessary for the production of taurine (*cf.* the anomalous effect of feeding cystine to cystinurics), but no extra taurine was excreted. Pyridoxine may be necessary for converting cystine to taurine (Blaschko, Datta and Harris, 1953) and 25 mg. extra pyridoxine was fed daily to Case 1 for three days, but there was no increase in taurine excretion. Acid hydrolysis of urine showed that taurine was not present in conjugated form except in traces; the quantity of conjugated taurine adsorbed by the acid resin, Zeo-Karb 225, was normal (*cf.* Woolf and Norman, 1957). The concentration of taurine in the blood was normal, or even above normal when the urinary concentration rose slightly; taurine in the blood was identified as in Woolf and Norman's (1957) analysis. The only conclusion is that in some unexplained way the diet increases the renal tubular reabsorption of taurine.

In Case 1 the urinary excretion of hydroxyproline, previously marked (*cf.* Woolf and Norman, 1957), fell almost to zero as soon as the diet was started. The excretion of proline and of all other amino-acids was unaffected except as discussed above.

Indolyllactic acid was present in all the specimens of urine examined before the children were placed on the diet, and indolylacetic acid could be detected in about half of them (*cf.* Armstrong and Robinson, 1954). Within a few days of starting the diet neither acid could be detected in the urine, in spite of the large amount of DL-tryptophan being given. Phenyllactic acid and the unidentified reducing keto-acid (Berry and Woolf, 1952) also vanished from the urine shortly after starting treatment, while the concentrations of phenolic acids and phenylacetylglutamine dropped to normal values.

The Diet

Basically the diet has differed very little from that described by Woolf *et al.* (1955). The major differences have been: (*a*) The reduction in the intake of cow's milk when the blood phenylalanine level, rather than urinary phenylpyruvic acid, was made the criterion (the amount of casein hydrolysate fed was raised to compensate for the diminished protein intake); (*b*) the adaptation of the diet for a very young infant; (*c*) modifications as the patients got older; (*d*) the addition of methionine.

The daily intake of cow's milk was between 60 and 120 ml. per day, providing an estimated 100 to 200 mg. of phenylalanine daily for children over 18 months of age. The daily requirements were higher during the first 18 months. Afterwards changes in phenylalanine requirement were slow for any given child, but there was some variation between one child and another. Potatoes were given to the older children in strictly controlled amounts, 2 oz. mashed potato being taken as equivalent to 1 oz. cow's milk in phenylalanine content.

Cases 1 and 8 presented a special problem as they were only 17 days old and 4 months old respectively when treatment was decided on. The soup, vegetables, bread, etc., of the older children had to be replaced by a thin liquid which had to contain, as far as possible, all the nutrients of human milk, except phenylalanine, in their correct concentrations. The greatest difficulty was in incorporating the fat; experiments with coconut oil and glyceryl monostearate were unsuccessful, the emulsion invariably breaking when the mixture with amino-acids, sugar, salts, etc. was sterilized. Eventually the fat was added as double cream and this was completely successful. The composition of the 'milk' is shown in Table 1 (Appendix).

The thick cream supplied a proportion of the protein required (for phenylalanine) and the rest was supplied by the cow's milk. A diet completely free from phenylalanine was never given to these very young infants, in contrast to the older phenylketonurics who were given a phenylalanine-free diet for a few days to bring the blood phenylalanine level down quickly before adding cow's milk. The amount of cow's milk fed to the young infants had to be increased frequently as it was repeatedly found insufficient to keep the blood phenylalanine level up to normal. At its maximum, when Case 8 was 7 months old and weighed 7·4 kg., the daily intake of cow's milk was 120 ml. in addition to 90 ml. of double cream, and slightly less for Case 1. Another

case, not reported here in detail, at 11 months required 200 ml. of cow's milk and 100 ml. of double cream daily to keep the blood phenylalanine level normal. After the eleventh month the phenylalanine requirements began to drop. Inositol and choline were given in such large amounts because they are present in milk (Robinson, 1951) though of unknown function. The salts were also added to give a mixture resembling the inorganic constituents of human milk and of the same *p*H, though the calcium phosphate had to be in suspension. Vitamin B_{12} was added as 'cytagon' oral syrup in preference to crude liver extract, and folic acid was added to the vitamin tablets (*cf.* Collins, Harper, Schreiber and Elvehjem, 1951).

As the children got older and could take a more solid diet than the original soup, some variety was introduced. The cow's milk was omitted from the soup, and was given with a cereal at breakfast. The 'soup' was made thicker, flavoured with tomato and given at the mid-day meal only, sometimes poured over potatoes, swedes, cabbage, etc., but more often as a separate course. Vegetables (except potatoes and pulses) were allowed freely. Stewed fruit, or a pudding (made from cornflour or sago with sugar, flavouring and colouring) followed; the parents were given a number of recipes. Bread, made from gluten-free wheat starch, with margarine and honey or jam was given at teatime and at other meals as required. Biscuits made from wheat starch, fat, sugar and flavouring were allowed freely, as were oranges and apples and sugar confectionery.

It is difficult to get much variety into the menu since all forms of protein are almost wholly barred. In spite of all efforts it is impossible to disguise completely the taste of the casein hydrolysate. It is remarkable that the children have taken the diet so well; there has been very little difficulty in getting any child to accept the diet in the first place, and they mostly continue to take it without any trouble —even the older children of fairly high I.Q. Some difficulty has sometimes arisen where a normal child in the same family awakens the phenylketonuric to the fact that her food differs from the normal sibling's, but this has always been smoothed over by the exercise of a little tact. A number of commercial firms have become interested in supplying a casein hydrolysate of better flavour, or in providing a ready mixed 'soup' powder, containing all the ingredients of the diet, to which the mother need only add hot water and flavouring.

DL-methionine was added to the children's diets when it was suspected that they were getting insufficient sulphur-containing amino-acids. Although this was shown to be a misinterpretation of the facts, DL-methionine is still added to the diet, a child over 1 year of age getting 1 g. daily. Casein is not very rich in sulphur-containing amino-acids, and hydrolysis and charcoal treatment removes the cystine; it seemed logical to provide an additional source of sulphur. Methionine was chosen in preference to cystine because methionine can replace cystine in the diet but not *vice versa*.

After the first few weeks the patients were all treated at home. The parents showed varying degrees of ability to cope with the special diet. Of the 11 patients, the parents of eight were fully cooperative. The parents of Case 7 refused to cooperate. In Case 4 there was very little attempt to keep to the diet. In Case 10 the child was quite obviously given forbidden foods on many occasions; a talk with the mother would result in a temporary drop in the urinary phenylalanine concentration, but sooner or later she lapsed. Case 2 also had an occasional lapse, shown by a temporary rise in urinary phenylalanine excretion; the child may have been taking food from the larder herself. Case 3 showed at one time a moderate rise in phenylalanine excretion that persisted and even increased in spite of cutting down her daily allowance of cow's milk and potatoes. Eventually phenylpyruvic acid appeared in the urine and her I.Q. remained stationary for six months, *i.e.*, progress, previously marked, ceased. It was only after close questioning that the parents, who were intelligent and cooperative, mentioned that the child was very fond of tea, drinking several cups a day. Each cup contained perhaps 60 ml. of milk. As soon as this beverage was omitted, phenylalanine excretion fell to normal and her I.Q. started to rise. In the other seven cases the parents seemed well able to make up the diet and repeated checks showed it was being adhered to. Thus in only two out of 10 cases did the parents seriously fail to keep to the diet.

Discussion

When Fölling (1934) first described phenylketonuria it was immediately apparent that this condition was an inborn error of metabolism closely analogous to those described by Garrod (1908, 1923). It has since been shown by Jervis (1953) that the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine in the normal liver, is absent from the liver of phenylketonurics. The simplest hypothesis is that in phenylketonurics the gene normally responsible for an essential stage in the synthesis of phenylalanine hydroxylase is replaced by a mutant gene incapable of this synthesis. Thus the inheritance of phenylketonuria as a recessive character is explicable if the patient

is assumed to be homozygous for the mutant gene. Probably all the abnormal biochemistry of phenylketonuria results from the absence of phenylalanine hydroxylase.

The almost invariable association of severe mental defect with phenylketonuria, and its frequent association with epilepsy, have been explained as being due to either a pleiotropic effect of the same recessive gene, or an intoxication by phenylalanine or one of its metabolites, or a deficiency of tyrosine due to its not having been formed from phenylalanine. All three theories have been put forward at various times and, to some extent, investigated, *e.g.*, by Jervis (1937, 1950), Borek, Brecher, Jervis and Waelsch (1950), Woolf *et al.* (1955), Cowie (1951a) and Woolf and Vulliamy (1951).

If the mental deficiency is due to an intoxication, whether by phenylalanine or by one of its abnormal metabolites formed as a result of a high concentration of phenylalanine in the cells, it might be reversible by giving a diet low in phenylalanine unless permanent mental damage has occurred. The success attending the giving of such a diet is reported above and confirms and extends previous reports of success (Woolf *et al.*, 1955; Bickel *et al.*, 1953; Armstrong and Tyler, 1955; Braude, 1956; Blainey and Gulliford, 1956; Horner and Streamer, 1956). This improvement in the mental state is evidence of the correctness of the intoxication hypothesis.

The clearest evidence of a mental effect of the diet is given by the curves of mental age plotted against chronological age (Figs. 1-4). The slope of this line at any given point is the progress rate of the child at that time (Woolf *et al.*, 1955). In most cases there was a sharp inflexion upwards as soon as the low-phenylalanine diet was started. This improvement has been maintained while the child stayed on the diet, *i.e.*, the curve did not return to its original slope; although often the slope has remained well below the mean for the population as a whole. This finding can be explained only as an effect of restricting the phenylalanine intake.

There is no evidence of a spontaneous increase in progress rate or intelligence quotient in untreated phenylketonuria; in fact all the evidence is that there is a steady decline in both, rapid at first and gradual later (*e.g.*, Cases 5 and 7). These children are normal at birth and signs of mental deficiency are usually first noted at an age of 6 months or later. By about 1 year the child is usually an idiot, and mental deterioration seems to continue thereafter at a reduced rate. It is estimated that the majority of all older untreated phenylketonurics have intelligence quotients below 30 and fewer than 1% have intelligence quotients over 70 (Penrose, 1951). The probability of finding a phenylketonuric of average intelligence is very low indeed. Apart from the cases reported above and others treated elsewhere, only two cases have come to our notice, one of a boy aged 6 with an I.Q. of 103, who will be reported elsewhere (Coates, Norman and Woolf, 1957), and one of a 6-year-old boy who scored 94 on some intelligence tests (Cowie, 1951b). It is unlikely that any considerable number of phenylketonurics of normal intelligence are not being detected because: (*a*) the ferric chloride test has been so widely used for urinary 'acetone bodies', it is unlikely that a strong green coloration would be overlooked or not reported, and (*b*) the shape of the distribution curve of intelligence quotient among phenylketonurics, with its mode at 10, indicates (unless it is bimodal) that very few indeed would come within the normal range (*cf.*, Larson, 1956). Thus there is only a very low probability that in Cases 1 or 2 the intelligence would be at its present level if untreated.

In addition to the effect on the intelligence, with all that this implies, the electroencephalogram has become more nearly normal in two cases after the child was placed on the diet and epileptic fits have ceased (Cases 4 and 10). The epilepsy, often closely resembling petit mal, which occurs in a proportion of phenylketonurics is unusually resistant to drug therapy and the success of the low-phenylalanine diet in controlling it is all the more striking. However, in Case 9 the diet did not control the fits and the E.E.G. showed little improvement. In Case 5, starting the phenylalanine-restricted diet seemed to cause major epilepsy leading to status epilepticus, and the return to a normal diet seemed to have the same effect, in each case two to four weeks after the change in the diet. Both these cases showed evidence of mental deterioration even while they were on the diet; the continuing epilepsy may well be partly or wholly responsible for this. Epilepsy is more common in phenylketonurics of low I.Q. than in high-grade ones, and the intellectual defect may be partly due to the epilepsy in these cases or both may be the expression of more severe intoxication. As in other causes of epilepsy, once the condition is well established it appears to be not always controlled by removal of the precipitating agent.

Among minor effects of the diet, the eczema-like skin condition frequently found in phenylketonurics clears up rapidly. The dramatic darkening of the hair is one of the most striking effects of the diet. The relative deficiency of melanin in hair, skin and eyes in phenylketonuria is well known (*cf.*, Cowie

and Penrose, 1951), and it has recently been shown that this is probably due to competitive inhibition of tyrosine oxidase by phenylalanine (Dancis and Balis, 1955). The inhibition is reversible *in vivo* by giving massive doses of tyrosine (Snyderman, Norton and Holt, 1955). It is not unexpected that the inhibition should also be reversible by reducing the phenylalanine concentration in the body by dietary means; the amounts of tyrosine given by us were insufficient of themselves to account for the hair darkening.

It is tempting to try to link this inhibition by phenylalanine of the formation of dihydroxyphenylalanine with the effects on the central nervous system, adrenaline and noradrenaline being synaptic transmission agents chemically related to dihydroxyphenylalanine. In fact, Weil-Malherbe (1955) has found that the concentrations of adrenaline and noradrenaline in the blood are unusually low in phenylketonuria. However, Pare, Sandler and Stacey (1957) have found that the serum concentration of 5-hydroxytryptamine, a neurohumoral agent chemically unrelated to dihydroxyphenylalanine, is also low in phenylketonuria and rises when a low phenylalanine diet is fed (Sandler and Stacey, 1957, private communication). It may be that the low blood concentrations of adrenaline, noradrenaline and 5-hydroxytryptamine are merely a reflection of a lowered level of activity of the central nervous system, and not due to a direct chemical inhibition of their formation.

In phenylketonuria the effects of the intoxication are not completely reversible. In almost every case the progress rate, although accelerated once the child was put on a low-phenylalanine diet, has been less than 100, suggesting that there is an irreversible component, as well as a reversible one, in the mental deterioration. Nor is this unexpected: from the age of a very few days the child has been subjected to the continuous action of a depressant substance—the period when the normal child is acquiring its first knowledge of the outer world, its first mastery of itself and its environment, is spent in a 'drugged' state. However completely the intoxicant is later removed, the effects of this time lost at a vital period will show in later years.

The brain is undergoing continuous structural development in the early months of life. (It is noteworthy that no consistent morphological changes in the brain have been reported to be associated with phenylketonuria.) It has been suggested (Hebb, 1949) that the neural mechanisms necessary for the earlier steps in learning may be altered by normal growth and development in such a way that they are not so readily available to an older child. This may explain why, in most of the cases considered here, although the brain has been restored to physiological normality by removal of an intoxicant, there is some impairment of the ability to learn. The lowering of the intelligence quotient in phenylketonuria is due to two factors: this irreversible component, and the immediate effect of the intoxication.

In Figs. 1-4 it can be seen that the slope of the curve of mental age plotted against chronological age is less than the average normal even after treatment has started. This reflects the permanent element of the mental deterioration. The time lag when treatment is started, *i.e.*, the difference between chronological and mental ages, is due to both temporary and permanent factors; it represents a gap between normal and phenylketonuric that may never be closed. From Fig. 1, curves 2 and 3, a temporary departure from the diet appears to result in a temporary flattening of the curve, but the slope returns to its previous value on resumption of the diet. We may tentatively conclude that a fairly short period of intoxication at the age of 4 or 5 years causes a reversible mental deterioration; nonetheless the time lag has been increased and the I.Q. consequently may always be lower than it would otherwise have been. Earlier in life, a period of intoxication increases the degree of permanent mental damage as is shown by the slope of the curve.

Cases 4 and 9 raise two interesting and perhaps related problems. Both children showed behaviour which could be called psychotic. In Case 4 this withdrawal most probably was the result of the 10 months in hospital, since on his return home he became more normal in his play and relationships. This withdrawal coincided with, and perhaps produced, a period when the mental age remained stationary though the diet was being kept to. The return to more normal behaviour at home led to a renewed but slow rise in mental age even though the diet was abandoned. Periods in hospital are known in general to depress the mental development of children (*e.g.*, Spitz, 1955). The deterioration in Case 9's emotional relationship seems to have a different origin. There have been no prolonged periods of separation from the mother, though the birth of twins has absorbed the mother's attention to some extent. The quality of the behaviour is more like that of a child with psychotic behaviour of organic origin. This observation can, perhaps, be correlated with the fact that the E.E.G. in Case 9 has remained abnormal, though in Case 4 it returned to normal on the diet. It seems possible that Case 4 may have suffered from a temporary psychosis of psychological origin, and Case 9 may have a

permanent psychotic condition, additional to the lowering of the intelligence, following brain damage which is observable also on the E.E.G. Case 11 is the only other case with an E.E.G. which has remained abnormal, though there have been no fits, and it is interesting that he has always cried and been very actively miserable on every visit to the hospital.

The mental deterioration in untreated phenylketonurics follows an approximately exponential curve; it is most rapid during the first few months of life, *e.g.*, Case 8, I.Q. 57 at 4 months, higher than the great majority of older phenylketonurics; after the second year it proceeds more slowly, but still measurably, *e.g.*, Case 7. Even in Case 1, where the diet low in phenylalanine was started by the fifth week, some slight degree of mental deterioration had already occurred and appears to have been arrested but not reversed. In Case 8 the diet, started at 4 months, appears to have prevented further deterioration though there is as yet no significant rise in the G.Q. As one would expect, the younger the child and the less the degree of mental damage (as measured by the I.Q.), the greater the effect of the diet. This indicates the necessity for diagnosing phenylketonuria and instituting treatment as early in life as possible. The test for phenylpyruvic acid in the urine is extremely simple,* and the implications of a positive result are most important.

We advocate that every child's urine should be tested at the age of 21 days. In the light of further experience it may be possible to shorten this period between birth and testing. The urine of a sib of a known case of phenylketonuria should be examined daily, as far as possible, from birth up to at least 3 weeks of age (perhaps using paper chromatography as well as the ferric chloride test) both for his own sake and to help to close a gap in our knowledge, since there is a one in four chance that he will be affected, and we know neither the age at which the blood phenylalanine level begins to rise nor the age at which phenylpyruvic acid first appears in the urine in affected cases.

If this scheme is followed, all future cases of phenylketonuria will be detected and treatment begun before the fifth week of life. We estimate that from 20 to 40 new cases are born every year in Great Britain, basing this on Munro's (1947) figure of two to six cases of phenylketonuria per 100,000 population, and the 600,000 live births every year. It is probable that the incidence is rather higher than Munro estimated, because his figures are based on the population of institutions for low-grade mental defectives and their relatives, and there is a small but appreciable number of phenylketonurics of too high a grade to be admitted to institutions (*e.g.*, Case 2; *cf.* Coates *et al.*, 1957). The local health authorities should work out the necessary administrative measures to see that health visitors collect and test the urine of every baby. A coloured card with instructions as to testing is being prepared.† Already one large local authority has asked one of us to talk on the subject to health visitors and midwives in the area.

Even in older children a worthwhile improvement often results from dietary treatment. It is obviously a gain even if a child's mental rating is raised only from idiot to imbecile level. As a rough guide we consider treatment worth initiating if the child is 2 years old or under and the G.Q. not less than 20, or 3 years old with a G.Q. of 30 or over, or 4 years old with a G.Q. of 40 or over. In any border-line cases it is probably wise to try six months' treatment with careful psychological testing at the beginning, at 3 months and at the end of this period. A decision would then be reached in the light of any improvement effected. It is also important to rule out any other form of brain disease. For example, in the presence of spasticity or any suggestion of birth trauma in the widest sense, investigations such as air studies should be undertaken to eliminate the possibility of structural brain damage of a gross type.

We do not know for how long the diet must be strictly adhered to. It may be impossible to relax it throughout life. On the other hand, once development of the brain has reached a stage where permanent mental damage is unlikely, a certain degree of intoxication resulting from some relaxation of the diet may be tolerable. However, from Case 3, it appears that 5 years is too early an age for this.

The effects of giving a normal diet, after the child had been on a low-phenylalanine intake, have been reported by Bickel *et al.* (1953) and by Armstrong and Tyler (1955). They both noted reversal of the previous improvement. In Case 5 above, the mental age actually started to decline, causing a marked decrease in I.Q., when her diet was changed from one low in phenylalanine to a normal one; previously her I.Q. had been maintained at a steady though very low level. Somewhat similar findings were noted in Case 4, but here

* To a fresh specimen of urine is added a little 5% ferric chloride solution. A green coloration, reaching a maximum within five minutes and fading only slowly, constitutes a positive result. Acidification is unnecessary and can invalidate the test. The ferric chloride can be spotted on to a wet napkin but this is much less reliable than the test-tube method.

† This may be obtained from the Secretary, The Hospital for Sick Children, Great Ormond Street, London, W.C.1, price 6d.

the results are complicated by other psychological factors.

None of the children considered here has been given any psychological treatment or tuition likely to affect the score in intelligence tests. All, except Case 4, have been treated at home and received the ordinary attention a child receives from parents who have not been instructed in any special teaching or training. Only one child, Case 3, has received part-time tuition from a trained teacher, and this for a limited period. Thus we can eliminate disturbing factors in evaluating the effect of the diet on mentality.

These children have special educational problems. As the child emerges from his semi-intoxicated state and begins to function more normally in the intellectual sphere, his capacity to learn is accelerated. Learning takes time, and his climb to a state nearer to his innate level will take several years and may involve some strain. Thus the child of imbecile level with a rising I.Q. may eventually need, not an occupation centre, but a school for educationally subnormal children, and even here full justice may require an open mind, for the child may be capable of travelling still further, in fact to the normal school. Each case should therefore be considered individually and sympathetically by education authorities, and re-assessed frequently so that suitable adjustments can be made in the type of education available to him.

A further question is whether definite psychological help, other than periodic testing of intelligence, should not be seriously considered. These children, while improving rapidly, need sympathetic handling. Some of them tend to be nervous and, having much to catch up educationally, and socially may need individual tuition, or remedial education, or even psychotherapy. It is possible that even more rapid progress might be obtained through attendance at a child guidance clinic or other centre for individual or group play therapy.

Summary

The results of treating 10 phenylketonurics with a diet low in phenylalanine are described.

In almost every case there was a sharp and significant rise in I.Q. The I.Q. continued to rise, the mental age plotted against chronological age showing a point of inflexion at the time the diet was started.

An infant treated from the age of 5 weeks has remained at I.Q. 88 for nearly two years, indicating that relatively slight deterioration had occurred during the five weeks before treatment. Mental deterioration (dementia) proceeds most rapidly in untreated cases during the first weeks of life, then gradually slows down, but is still continuing appreciably at 2 years of age.

As it seems likely that mental deterioration in this condition can be prevented by early treatment, we suggest that every infant's urine be tested with ferric chloride at the age of 21 days (though this age may have to be modified), and treatment instituted immediately if a positive reaction is obtained.

It is important to keep the blood phenylalanine concentration at the normal level. If it is too high the child's progress slows down measurably, if too low, the child ceases to grow or thrive. The diet must supply all essential nutrients.

The success attending the use of this diet confirms the theory that the mental deficiency in phenylketonuria is the result of intoxication by phenylalanine or one of its abnormal metabolites.

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Addendum

In November, 1957, Case 9 had an attack of tonsillitis and refused all food for five days. At the end of this period her urine was found to contain phenylpyruvic acid in a concentration approaching that found in untreated cases of phenylketonuria, and her blood phenylalanine level was also very high.

The most likely explanation is that phenylalanine was released in the proportion relative to the other amino-acids in which it occurs in the tissue proteins which are spontaneously breaking down. This would be, of course, the ideally balanced amino-acid mixture for a normal person (and is approached by ordinary dietary proteins), but the phenylketonuric, owing to the absence of the enzyme phenylalanine hydroxylase, cannot catabolize the phenylalanine released from the tissues and therefore, in the fasting state, it accumulates in the blood and tissues. The low phenylalanine diet provides the other amino-acids in proportions giving a balanced mixture for a phenylketonuric, permitting all the phenylalanine released by tissue breakdown to be used in the synthesis of new tissue protein, and allowing for growth and for the small loss of phenylalanine in the urine and by reactions not involving phenylalanine hydroxylase.

APPENDIX

The following items of the diet can be provided by the National Health Service: Casein hydrolysate, tyrosine, tryptophan, methionine, calcium hydrogen phosphate, the items listed in Table 2, a mixture of salts in solution, namely, potassium chloride, sodium chloride,* magnesium sulphate, potassium iodide,* sodium citrate,* citric acid.*

* Only in the case of infants under 1 year old.

The parents have to buy sucrose, cow's milk, gluten-free wheat starch, kosher margarine, double cream, iodized salt, tomato juice, fruit, cornflour, sago, flavourings, vegetables, breakfast cereal, honey, jam and sweets.

TABLE 1

COMPOSITION OF 'MILK' GIVEN TO CASES 1 AND 8

Ingredient	Daily Intake
Casein hydrolysate*	24 g.
L-Tyrosine	2 g.
DL-Tryptophan	1 g.
DL-Methionine	1 g.
Sucrose	90 g.
Cow's milk	0 to 200 ml.
Double cream†	85 ml.
Calcium hydrogen phosphate	0·71 g.
Potassium chloride	0·65 g.
Sodium chloride	0·016 g.
Magnesium sulphate	0·165 g.
Sodium citrate	0·177 g.
Potassium iodide	0·00013 g.
Citric acid	0·08 g.
Water	to 850 ml.

* Acid hydrolysed casein passed through charcoal to remove phenylalanine and tyrosine.
† 48% fat, 1·7% protein.

TABLE 2

DAILY INTAKE OF SUPPLEMENTS TO ABOVE 'MILK'

Ingredient	Daily Intake
Choline chloride	100 mg.
Inositol	216 mg.
Vitamin B_{12}	4 µg.
Aneurine hydrochloride	0·5 mg.
Riboflavine	0·5 mg.
Pyridoxine	0·33 mg.
Nicotinamide	3·33 mg.
Ascorbic acid	40 mg.
α-Tocopherol	0·33 mg.
Acetomenaphthone	0·5 mg.
Biotin	0·17 mg.
Folic acid	0·25 mg.
Vitamin A	3,000 I.U.
Vitamin D	500 I.U.
Ferrous sulphate	0·15 g.
Manganous sulphate	0·0008 g.
Zinc sulphate	0·0014 g.
Cupric sulphate	0·003 g.

PARATHYROID ADENOMA IN A CHILD PRESENTING AS RICKETS

BY

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(RECEIVED FOR PUBLICATION JULY 4, 1957)

Primary hyperparathyroidism in childhood is rare. Anspach and Clifton found only 12 cases up to 1939 and since then a few cases in children have been reported by Pugh (1946), Tsumori, Jensen, Hunnicutt, Foreman and Kinsell (1955), Crawford, Stefanelli and Alvarez (1956); these have in general, shown the changes typical of the adult.

The case described here is thought worthy of notice, not only in view of the age, but also because the degree of renal involvement and the radiological features were misleading at the time; in addition, as Dent and Hodson (1954) have stated, primary parathyroid disease in childhood may help to elucidate further the mode of action of parathyroid hormone.

Case Report

John W., aged 12, was first seen in March, 1956, with a five months' history of lethargy, vomiting, anorexia, thirst and polyuria, following a fracture to the left radius and ulna. This fracture resulted from a fall while wrestling with another boy and no obvious radiological abnormality was seen in the bone. No definite clinical abnormality was detected at this time. His blood pressure was 100/60 mm. Hg and his urine was normal apart from 4 white blood cells per high-power field.

FIGS. 1.—Radiographs showing changes of late rickets.

His symptoms continued and a few months later he complained of pain in the left ankle, which on radiographs showed changes of late rickets (Figs. 1 and 2). He was therefore admitted for further study 17 months after the onset of symptoms. The muscles were flabby, the skin slightly pigmented and his blood pressure had risen to 130/100 mm. Hg.

Investigations gave the following results:

There was no albumin in the urine, but 4-6 white blood cells per high-power field. The specific gravity after a 12-hour fluid fast was 1010. Other results were as follows:

Blood	March 11, 1957	March 20, 1957	April 3, 1957
Calcium ..	14 mg. %	16 mg. %	17·5 mg. %
Phosphorus	3·8 mg. %	2·1 mg. %	4·7 mg. %
Urea ..	46 mg. %	40 mg. %	28 mg. %
CO_2 ..	40 vol. %	52 vol. %	48 vol. %

(Soon after admission he developed acute appendicitis; this was treated by appendicectomy and at this time his blood urea rose to 80 mg. % and his alkali reserve fell to 20 vol. %.)

Excretion pyelography showed poor concentration of the dye but normal calyces were seen.

Urine excretion studies on a low-calcium diet (less than 100 mg. calcium per day) gave 0·41 g. calcium per day and 1·23 g. phosphorus per day.

The calcium content of C.S.F. was 5·5 mg. %. According to Howard, Carey, Rubin and Levine (1949) a level below 6·0 mg. % in the presence of hypercalcaemia suggests primary hyperparathyroidism.

FIG. 2.—Radiographs showing changes of late rickets.

The principal features radiologically were generalized osteoporosis and subperiosteal erosions, particularly in the phalanges and the upper medial and lower posterior margins of the tibiae (see Fig. 2). The confusing element was the rachitic changes at the lower radial, ulnar, tibial

FIG. 3.—Radiographs showing changes of late rickets.

and fibular metaphyses on both sides (see Figs. 1, 2 and 3). A dental radiograph was also taken and showed intact lamina dura (as also did Tsumori and his colleagues' (1955) child of 10 with primary hyperparathyroid disease), a feature pointing against parathyroid hyperactivity of any duration.

The differential diagnosis between primary and secondary hyperparathyroidism has been summarized by Dent and Hodson (1954); this boy's biochemical findings fell neatly into the primary group, while the radiological features were equally typical of secondary or renal osteodystrophy, the impaired kidney function also tending to support the latter diagnosis. It was, however, clear that if a parathyroid tumour were suspected, the neck must be explored.

At operation an oblong tumour, 1 in. by ¾ in., was removed from behind the left lower pole of the thyroid, which on histology was found to be an adenoma of the wasserhelle cells (Figs. 4 and 5). Both sides of the neck were explored without any further abnormality being encountered.

The post-operative course was uneventful, the serum calcium level falling to 8·9 mg. % by the end of a week and the urinary calcium on a high calcium intake falling to below 0·05 g. per day.

When last seen two months after operation he was in good health with a blood pressure of 130/80 mm. Hg and normal calcium and phosphorus levels in the serum.

Discussion

A review of the literature makes it clear that quite severe renal impairment can occur as the result of primary hyperparathyroidism, atypical cases presenting as diabetes insipidus (Albright and Reifenstein, 1948) or hypertension (Race, 1952).

We should not therefore have been much influenced by the failure of this boy's kidneys to concentrate. We were, however, considerably disturbed by the radiological appearances of rickets, as Dent and Hodson (1954) imply that the essential difference between primary hyperparathyroidism and the secondary form due to renal disease is that in the former there is no sign of rachitic change. This is instanced by the 8-year-old boy reported by Pugh (1946) and similar statements are made by Albright and Reifenstein (1948) and Snapper (1949). However, Caffey (1950) states that in pre-adolescent primary hyperparathyroidism 'rachitic-like changes in the metaphyses have been described', presumably referring to the cases of Duken (1928) and Anspach

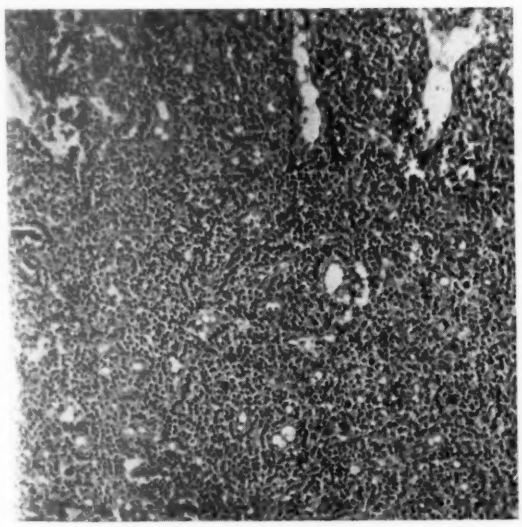

Fig. 4.—×90.

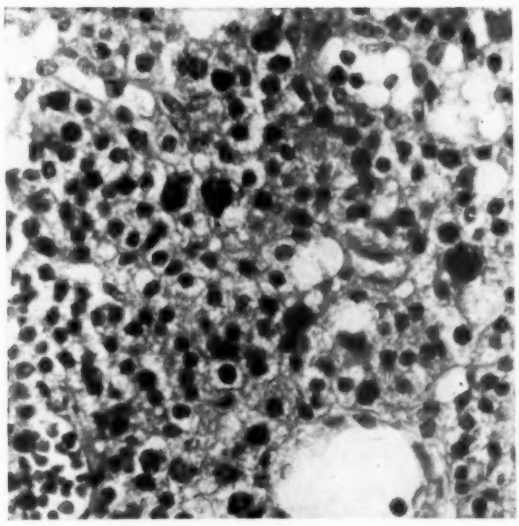

Fig. 5.—×375.

FIGS. 4 and 5.—Photomicrographs of the adenoma. Haematoxylin and eosin.

and Clifton (1939). Brailsford (1953) too states that in hyperparathyroidism before adolescence the radiographic appearance may be similar to type B renal rickets and he illustrates a case of primary hyperparathyroidism with rachitic changes in the lower ends of the radius and ulna.

Hunter and Turnbull (1931) differentiated the bone histology resulting from primary hyperparathyroidism, in which there is osteoporosis and no increase in osteoid tissue, from that of osteomalacia and rickets where osteoid is increased. They explained that in Schmorl's (1926) cases, where osteomalacia co-existed with hyperparathyroidism, the dietary state in Germany at that time led to the widespread occurrence of both osteomalacia and rickets in the general population. Such is unlikely to be the explanation in our case, as since infancy he regularly imbibed 2 to 3 pints of milk daily and took one teaspoonful of cod-liver oil throughout the winter months. The fact that he developed rickets on such a diet suggests perhaps that the phosphate diuretic effect of the parathyroid hormone predominated over its osteoclastic effect upon the bone. He had been growing 3 in. a year up to the time of his illness and any tendency towards a negative calcium or phosphorus balance might be expected to precipitate a rachitic change at the epiphyses. It does not seem possible to invoke an acidosis as the cause in view of the high serum calcium levels and the normal alkali reserve.

Summary

A boy of 12 presenting with radiological rickets was found to have the biochemical findings of primary hyperparathyroidism. This was confirmed by removal of a parathyroid adenoma at operation. It appears that radiological rickets can occur in primary hyperparathyroidism without primary renal disease or acidosis.

We are indebted to Dr. A. Booth for permission to reproduce the early radiographs, to Dr. W. H. Caldwell for the histological report on the tumour, to Mr. S. Smith for the biochemical investigations and to Mr. A. J. Higgs for the photomicrographs.

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ACROMEGALY IN A GIRL OF 8 YEARS

BY

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(RECEIVED FOR PUBLICATION JUNE 21, 1957)

Pierre Marie in 1886 first suggested the name acromegaly for a clinical condition associated with enlargement of the extremities (ἀκρα) which he had observed in two women aged 37 and 54 years. Marie reviewed the literature and found records of five male patients (two of whom were brothers) with similar features; the earliest of these descriptions concerned a man of 39 years reported by Saucerotte (1772). Marie also discussed the differential diagnosis of acromegaly from myxoedema, Paget's disease of bone (osteitis deformans) and leontiasis ossea of Virchow.

Although Saucerotte's account is probably the earliest medical description of acromegaly, the condition was well known to ancient writers. For example, the height of Goliath of Gath (1 Samuel 17. 4) was 6 cubits and a span (9½ ft.) and the record suggests that he may have suffered from a pituitary tumour which caused bitemporal hemianopia and so he was unable to see the stone slung at him by David. It is also of interest that Goliath's son was a man of great stature (2 Samuel 22. 20) and that he had polydactyly (six fingers on each hand and six toes on each foot); Goliath's brother was also a giant and the staff of his spear was like a weaver's beam (2 Samuel 22. 19).

The first paper suggesting a relationship between acromegaly and the pituitary gland was that of Verga (1864) of Milan. He reported the necropsy findings of a woman of 59 years who began to develop evidence of acromegaly at the age of 35 years; the post-mortem examination revealed a tumour extending from the sella turcica and compressing the optic nerves.

Acromegaly is exceedingly rare and is especially uncommon in childhood. Atkinson (1931) reviewed the world literature from 1890 to 1929 and found 15 boys and 10 girls under the age of 15 years suffering from acromegaly; during the past 25 years a few cases have been reported (Schlesinger, 1931; Behrens and Barr, 1932; Seale, 1934 and 1935; Hurxthal, 1943). The only previous case recorded in the *Archives of Disease in Childhood* since this journal was first published in 1926 concerns a boy of 6 years who lived in Brno (Traub, 1939) and showed acromegalic gigantism associated with bony changes in the right hip, tarsal scaphoids, metatarsals and vertebral bodies.

Case Report

G.O. was born on August 23, 1947, after a normal pregnancy and delivery. She weighed 7½ lb. at birth and developed normally until the age of 5 years when she had a mild attack of whooping cough. After this illness her mother noticed that she tired easily and that she was putting on weight excessively. It was not until two years later that the symptoms became more obvious. She consulted her family doctor (Dr. W. Jones Morris) in July, 1954, when she was 6 years 11 months old because of persistent nasal catarrh and he observed the acromegalic features. Her height at this time was 54½ inches. Her general health was good, her appetite was rather excessive, but she did not complain of visual disturbances (she had worn glasses from the age of 3 years), headaches or vomiting. A study of family photographs suggests that acromegaly had been present for some years. A photograph of the patient with her elder sister and younger brother taken when she was 3 years old did not show the features of acromegaly (Fig. 1) but a photograph taken when her brother was 4 years old and she was 5½ years old shows the enlarged hands and abnormal facial appearance of acromegaly (Fig. 2).

She was admitted to Alder Hey Children's Hospital, Liverpool, in February, 1956, for further investigation.

On admission (aged 8½ years) she weighed 116 lb., her height was 60 inches (height-age of 12½ years) and head circumference was 22 in. She was a heavily-built, coarse-featured child, with black hair, bushy eyebrows and the typical features of acromegaly. There was slight but definite generalized pigmentation of the skin, and pigmentation was especially marked in the axillae, groins, areolae and umbilical area. There was no axillary hair and no breast enlargement, but a small amount of pubic hair. There were no abnormal signs in the heart or lungs, blood pressure was 125/75 mm. Hg, and the abdomen was enlarged due to deposition of subcutaneous fat. Examination of the central nervous system, including optic fundi, was negative.

Table 1 records the measurements made of the patient, and of a girl one year older who was in the ward at the same time for investigation of 'dizzy spells'.

Further comparison is afforded by photographs of the hands (Fig. 3) and feet (Fig. 4), and by a full-length

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 1.—Patient (extreme right) at age of 3 years with brother and sister.

FIG. 2.—Patient at age of 5½ years with brother.

FIG. 3.—Right hand of patient and control.

FIG. 4.—Left foot of patient and control.

FIG. 5.—Full-length photograph of patient and control.

TABLE 1
MEASUREMENTS COMPARED WITH THOSE OF A CONTROL

	Control	Patient
Date of birth	23.6.46	28.8.47
Age (March, 1956)	9 years 9 months	8 years 7 months
Weight	67 lb. 4 oz. (50th percentile)	116 lb. 2 oz.
Height	51½ in. (50th percentile)	60 in. (height age 12½ yr.)
Upper measurement	26 in. (normal)	31½ in. (normal 26)
Lower measurement	25½ in. (normal)	28½ in. (normal 25)
Ratio upper/lower	1 to 1	1·1/1
Span	50½ in. (normal 52)	59 in. (normal 50)
Head circumference	21 in. (normal)	22 in. (normal 21)
Bone age	Same as chronological age	Same as chronological age

TABLE 2
MEASUREMENTS OF PATIENT'S FAMILY

	Height	Weight
Father	5 ft. 8 in.	160 lb.
Mother	5 ft. 3 in.	98 lb. 6 oz.
Sister (aged 10 yr.)	4 ft. 7 in.	67 lb. 8 oz.
Brother (aged 7 yr.)	4 ft. 1 in.	58 lb. 12 oz.

photograph (Fig. 5). The height and weight of other members of the patient's family are recorded in Table 2.

Investigations. Urine was of *p*H 5·5 and specific gravity 1020. No albumin, no reducing substances and nothing abnormal was seen in a centrifuged deposit.

Blood urea was 27 mg. %.

A blood count gave Hb 78% (11·5 g. %), leucocytes 9,000 per c.mm. (normal differential count).

Serum protein was 6·8 g. %, serum calcium 5·0 mEq/l., serum phosphorus 6·8 mg. %, serum alkaline phosphatase 14 K-A units %, serum potassium 4 mEq/l., serum cholesterol 190 mg. %, alkali reserve 19 mEq/l.

A glucose tolerance test gave the fasting blood sugar 100 mg. %, and half an hour after 35 g. glucose 130 mg. %, one hour 130 mg. %, two hours 140 mg. % and three hours 160 mg. %.

An insulin tolerance test gave the fasting blood sugar 107 mg., 20 minutes after 6 units of insulin 85 mg. %, 30 minutes 85 mg. %, 45 minutes 112 mg. %, one hour 95 mg. %, two hours 110 mg. %.

The total 17-ketosteroid content of a 24-hourly collection of urine was 2·8 mg. (average 0·3 to 1·99 mg.). The total 17 ketogenic steroids (corticosteroids) content of a 24-hourly collection of urine was 4·22 mg. (average 0·3 to 1·99 mg.).

An eosinophil test before intramuscular injection of A.C.T.H. gave 238 eosinophils per c.mm., after one hour 241, two hours 155, three hours 113, four hours 113.

Radiographs of the wrists and elbows show a bone

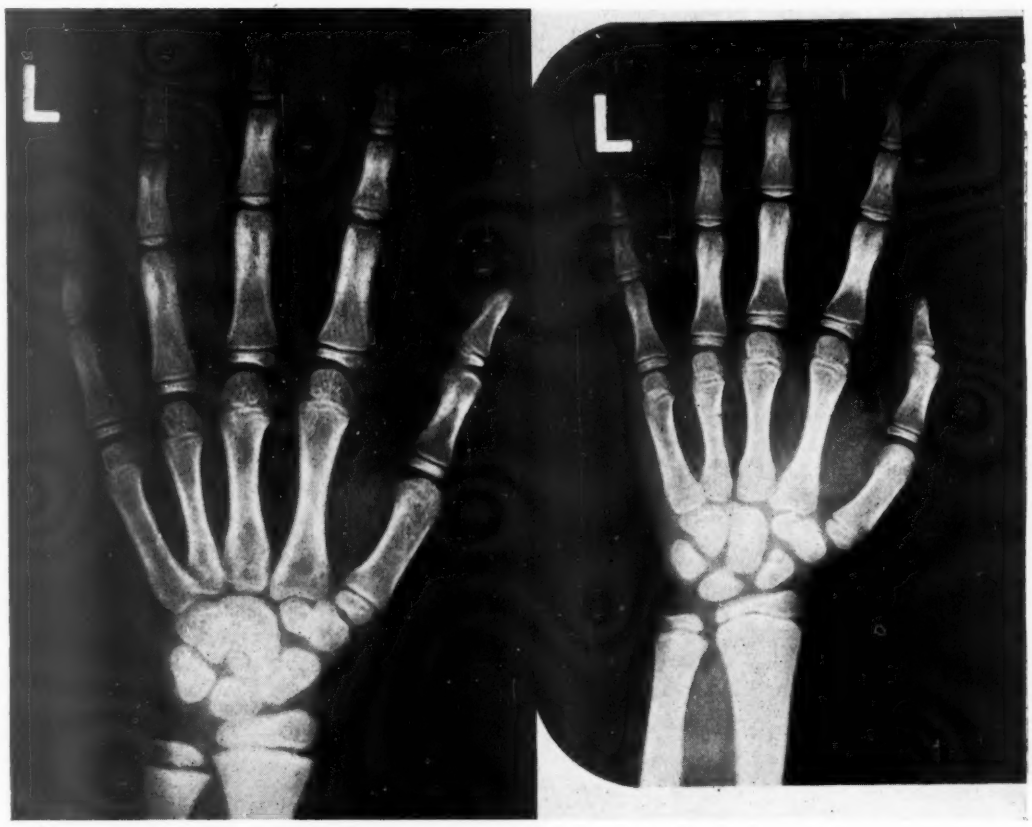

FIG. 6.—Radiograph of left wrist of patient and control.

age of 8 to 9 years (Fig. 6). The sella turcica was larger and deeper than that of the control (Fig. 7). No destructive changes were shown and there was no evidence of intracranial calcification.

An intravenous pyelogram was normal.

At rest an E.E.G. (Fig. 8) showed an irregular 9 per second alpha rhythm, and a considerable amount of slow activity within theta and delta ranges. There was no significant change on hyperventilation or on photic stimulation. The slow activity was very prominent and the delta activity was outside the limits of normal for a child of this age (report by Dr. R. R. Hughes).

A urinary nitrogen excretion test was carried out over a period of two weeks. The patient excreted 4·5 g. N_2 daily in urine, whereas a control excreted 7·2 g. per day.

The visual fields were entirely normal, and central colours also normal.

FIG. 7.—Radiographs of pituitary fossa of patient and control.

The patient was under observation in hospital for 11 weeks and during this period her height increased from 60 to 60½ in. and weight increased from 116 lb. 2 oz. to 125 lb. 4 oz. During this time the optic fundi remained normal, and she did not suffer from headache, vomiting or visual disturbance. She was seen, as an out-patient, by a radiotherapist (Dr. D. M. Fraser) who reported: 'I agree with you that acromegalic gigantism is the most probable diagnosis but I do not think that we should be justified in giving radiotherapy to the pituitary without more positive evidence of the presence of a tumour.'

In view of her continued growth and the embarrassment it caused her, particularly at school, it was decided to give oestrogens in an effort to promote epiphyseal fusion and thus prevent further excessive

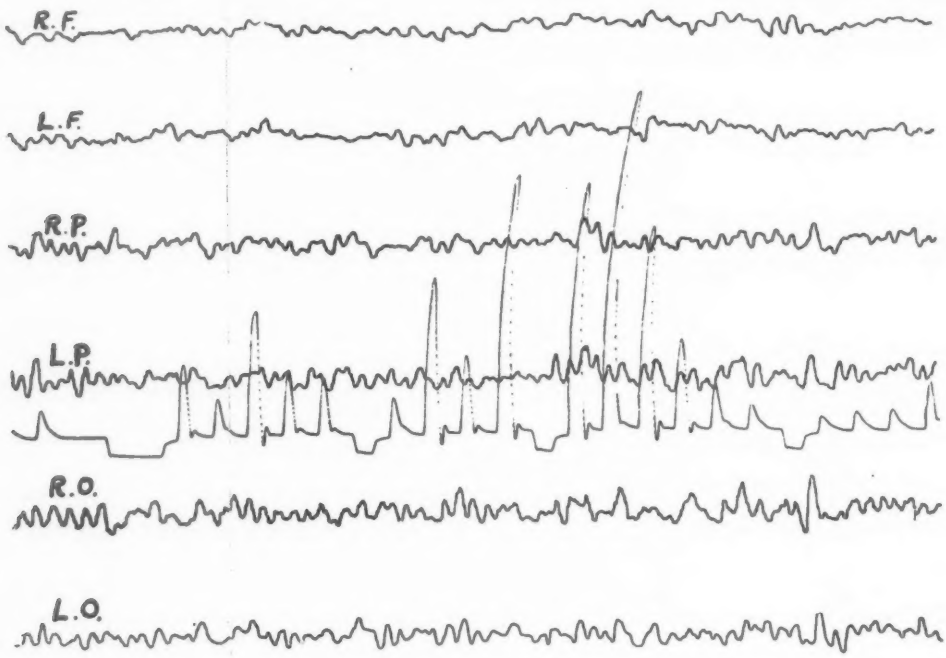

FIG. 8.—Electro-encephalogram.

FIGS. 9A and 9B.—Ventriculogram.

growth of the long bones. She received stilboestrol, 1 mg. daily, for three weeks, and then 1 mg. twice daily for three weeks. It was discontinued because of vomiting and severe headaches. Menstrual bleeding started one week after stilboestrol was stopped and bleeding continued for four days. She was readmitted to hospital on September 24, 1956, because of increasingly severe headaches in the frontal and occipital regions, and vomiting several times daily.

The fundi were examined and bilateral papilloedema of about 3 dioptres swelling was observed. She was seen by Mr. Hannah (neurosurgeon) who agreed to relieve the raised intracranial tension surgically. A ventriculogram (Fig. 9A and 9B) showed evidence of a large suprasellar lesion which was partially blocking the ventricles. It was felt that a direct approach to the tumour was fraught with danger and it was decided to perform a Torkildsen's operation, making a short circuit between the lateral ventricle and the cisterna magna. The symptoms were relieved after operation and she was then given *x*-ray therapy over a period of four weeks to a tumour dose of 3,000 roentgen units. At a follow-up examination on February 18, 1957, her general condition was satisfactory, she had not suffered from headaches, the visual fields were normal, and the papilloedema had completely subsided. The acromegalic features were not more marked.

Discussion

The diagnosis of pituitary gigantism is founded upon the clinical and radiological manifestations Talbot, Sobel, McArthur and Crawford (1952) have described the main clinical features as follows: (*a*) Rapid growth of the skeleton and supporting mesenchymal structures; (*b*) no acceleration of skeletal maturation; (*c*) usually no gross evidence of hyperthyroidism, hyperadrenocorticism or hypergonadism; (*d*) occasionally signs of an expanding lesion in the region of the pituitary.

(*a*) The patient reported in this paper shows these clinical features. Growth has been rapid from about 5 years of age, and her height was 54½ in. at the age of 7 years (height age of 10½ years) and 60 in. at 8½ years (height age of 12½ years). (*b*) The excessive growth is due to excessive production of pituitary growth hormone and this hormone does not cause early skeletal maturation or closure of epiphyses. The bone age of this patient was the same as her chronological age. (*c*) There was no clinical evidence of overactivity of the thyroid, adrenal or sex glands and the following investigations support the clinical findings: serum cholesterol normal, excretion of 17 ketosteroids only slightly above the average normal, response to A.C.T.H. normal, blood electrolytes normal. (*d*) The patient also showed clinical evidence of an expanding intracranial lesion (headache, vomiting, papilloedema) and this was confirmed by encephalography.

In addition to these main clinical features, the diagnosis is supported by haematological and radiological abnormalities. The glucose tolerance curve was of the diabetic type and the patient showed insulin resistance. There was also evidence from balance studies of retention of nitrogen (pituitary growth hormone increases the utilization of amino-acids for synthesis of tissue proteins, causing thereby retention of nitrogen). Wilkins (1950) states that the finding of a high serum phosphorus level of the order of 5 to 6 mg. % may be valuable in confirming the diagnosis of hyperpituitarism and in this patient the serum phosphorus level was 6·8 mg.%. Patients with pituitary gigantism sometimes show radiological changes of the terminal phalanges, cancellous tufts develop, and small spaces of bone may be observed. This patient showed cancellous tufting of some of the terminal phalanges. Seale (1935) reported an eosinophilia

(12 to 16%) in an acromegalic boy of 12 years but could find no reports of similar blood changes; the blood count of our patient showed no increase of eosinophil cells.

The treatment recommended for pituitary gigantism will vary with the severity of the disease but involves either surgery, irradiation or hormones.

Surgical removal of an eosinophil tumour of the pituitary gland is a difficult procedure and the mortality rate is high. Surgical treatment is usually restricted, as in this patient, to relief of intracranial tension by a short circuit operation, especially when vision is threatened. Irradiation of the sella turcica is the most usual form of therapy and is often carried out (as in this patient) after relief of intracranial tension by surgical means. There is a risk of damage to other pituitary cells, and after radiotherapy symptoms of diabetes insipidus may be observed.

The use of hormones to hasten bone maturation and epiphyseal fusion seems a rational form of therapy. Testosterone or stilboestrol hasten epiphyseal fusion and also inhibit the secretion of pituitary hormones. This patient received stilboestrol for a short period only but there was some radiological evidence to suggest that bone maturation was hastened even by such a short course of therapy. Other hormones, e.g., posterior pituitary extract, may also be required to control the symptoms of diabetes insipidus which may develop either because of the pressure of a rapidly growing eosinophil tumour on the posterior pituitary gland, or after irradiation of the sella turcica.

Summary

The clinical features and results of investigations of a girl of 8 years suffering from acromegaly are recorded.

The diagnosis and treatment of this endocrine disorder are discussed.

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MALIGNANT NON-CHROMAFFIN PARAGANGLIOMA OF THE THIGH

BY

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Within recent years it has become recognized that some tumours arising in skeletal muscle have a close resemblance histologically to tumours of non-chromaffin paraganglia such as the carotid body and glomus jugulare (Smetana and Scott, 1951). Such tumours are rare and have previously been designated granular cell myoblastomata or, more recently, alveolar soft-part sarcomas (Christopherson, Foote and Stewart, 1952). They occur mainly in children and young adults and are often malignant.

The case recorded here is that of a boy who developed a tumour of the left rectus femoris muscle, which recurred after local excision and subsequently gave rise to widespread metastases from which he died a year later.

Case Report

J.T., a boy aged 6 years, attended the Royal Hospital for Sick Children, Edinburgh, in June, 1950, with the complaint of a swelling in the front of the left thigh for three weeks. It had been gradually increasing in size but had given rise to no symptoms.

The swelling was excised locally. He remained well for eight months but then complained of frontal headaches and vomiting. He was found to have bilateral papilloedema and raised intracranial pressure due to a space-occupying lesion in the posterior part of the left cerebral hemisphere. Left occipital craniotomy and decompression were performed. He gradually deteriorated, with herniation of the brain through the craniotomy and paraplegia as a result of spinal metastases. The tumour recurred in the front of the left thigh and there was lymphatic spread to the left inguinal nodes.

Morbid Anatomy

The primary tumour in the left rectus femoris muscle measured $7 \times 3 \times 3$ cm. It was oval, fleshy and generally white with several pale pink areas (Fig. 1). It was embedded in muscle and its margin was well defined except in one region where it appeared to be infiltrating.

At necropsy a year later, the tumour had recurred locally and formed a large, fleshy mass, $15 \times 5 \times 4$ cm.,

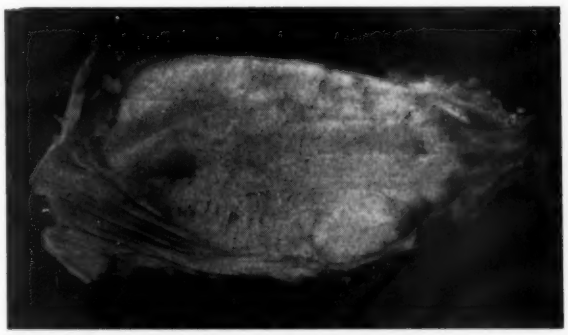

FIG. 1.—The primary tumour in the left rectus femoris muscle. About actual size.

adherent to the femoral periosteum. The left inguinal lymph nodes were enlarged and replaced by tumour. Secondary deposits were present in the liver, lungs, vertebral column and spinal cord, brain (Fig. 2), skull, palate and the medulla of the right adrenal gland. In all these situations except the brain the metastatic deposits were similar macroscopically to the original tumour in the thigh. The large neoplastic mass in the brain differed in that

FIG. 2.—Large secondary deposit in posterior parieto-temporal region of left cerebral hemisphere. Note the extensive haemorrhage.

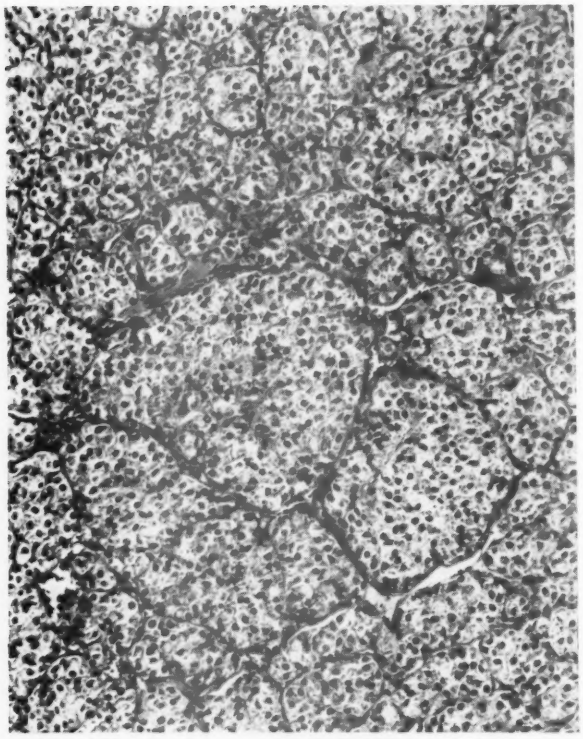

FIG. 3.—Primary tumour composed of discrete groups of granular cells. Note the vascular channels in several areas. H. & E. × 120.

widespread necrosis and haemorrhage had occurred. All epithelial tissues were examined with particular care to exclude a possible primary growth other than that in the thigh muscle.

Histology

Both primary and secondary tumours showed an identical histological pattern which is very characteristic and striking. The tumour cells were arranged in discrete groups which were enclosed by delicate, but usually well defined collagen fibres (Fig. 3). In many areas, these cell groups were separated from each other by vascular channels the walls of which were formed by the limiting collagenous membranes with an inner layer of extremely flattened endothelial cells (Figs. 4 and 5). These vascular spaces sometimes contained blood (Fig. 4), but were more often empty (Fig. 5). In the secondary deposit in the brain they were very large and engorged with blood. This delicate layer of endothelium was sometimes extremely thin and in places deficient (Fig. 5) so that tumour cells bulged into the lumina.

The neoplastic cells were large and polyhedral with indistinct cell boundaries and coarsely granular eosinophilic cytoplasm. The nuclei were large, variable in position and usually vesicular. Many contained prominent nucleoli. Mitotic figures were scanty. A striking feature in several areas was the production of a pseudo-acinar structure by degeneration of the central cells in the tumour masses (Fig. 6). Invasion of veins was observed in the primary tumour (Fig. 6).

Discussion

Tumours of this type have usually been classified as granular cell myoblastomata because of their relationship to skeletal muscle and granularity of the cytoplasm of the neoplastic cells. They can be readily identified by their distinctive histological pattern in the illustrations of several cases reported as granular cell myoblastomata, *e.g.*, Case 6 of Klemperer (1934), Case 4 of Horn and Stout (1943) and the case of Schwidde, Meyers and Sweeney (1951). Horn and Stout noted the striking pseudo alveolar structure of this group and used the term 'organoid' granular cell myoblastoma to describe them. Christopherson *et al.* (1952) reported 12

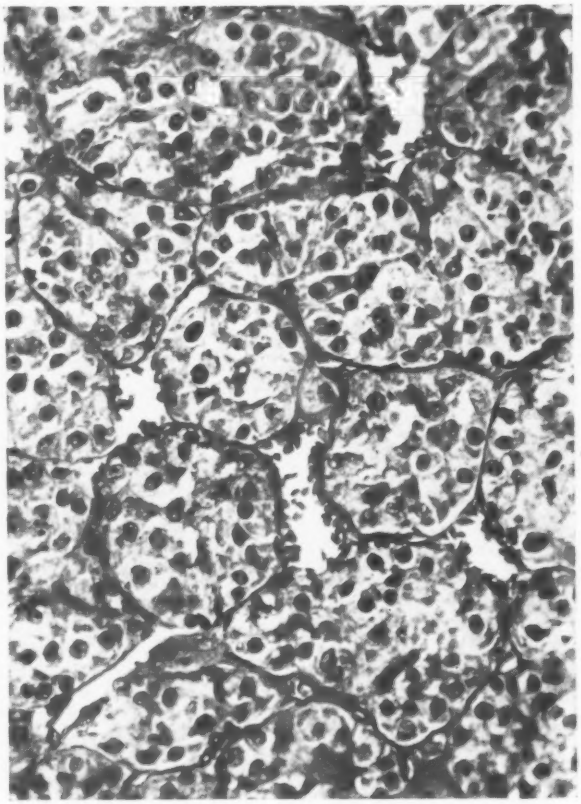

FIG. 4.—Delicate membranes of connective tissue enclose the groups of tumour cells. Several vascular channels containing red blood cells also present. H. & E. × 300.

tumours of this type, mainly in young adults and arising in skeletal muscle; 50% of them metastasized. They drew attention to their resemblance to paragangliomata but knew of no identification of any paraganglionic tissue in the extremities. They termed them alveolar soft-part sarcomas.

Smetana and Scott (1951) collected 14 examples of this tumour and showed that there was a close similarity to tumours of the carotid body and glomus jugulare. They considered they were paragangliomata and to support this view provided illustrations in their paper of structures removed from the vicinity of the large femoral vessels in Hunter's canal which they interpreted as normal paraganglionic tissue. Since then further examples have been described (Randall and Walter, 1954; Hicks and Leitch, 1955). Willis (1953) reported that he had seen five such tumours and was of the opinion that they were paragangliomata.

We agree with Smetana and Scott that these tumours are most probably non-chromaffin paragangliomata because of their striking resemblance to tumours of undoubted paraganglia, but conclusive proof of their origin must await confirmation of the presence of normal paraganglia in the limbs. We have attempted, without success so far, to identify such structures in the lower limbs of children and adults at necropsy.

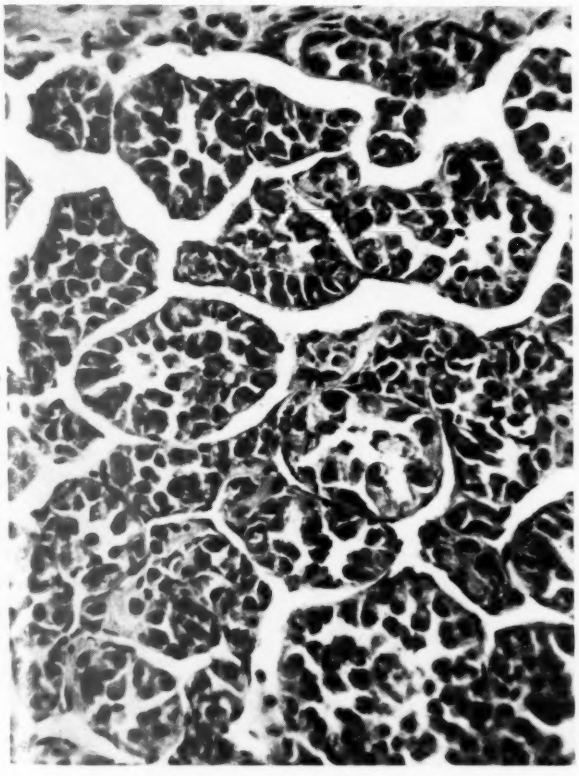

FIG. 5.—The endothelial lining of the vascular channels is extremely thin and deficient in places. H. & E. × 270.

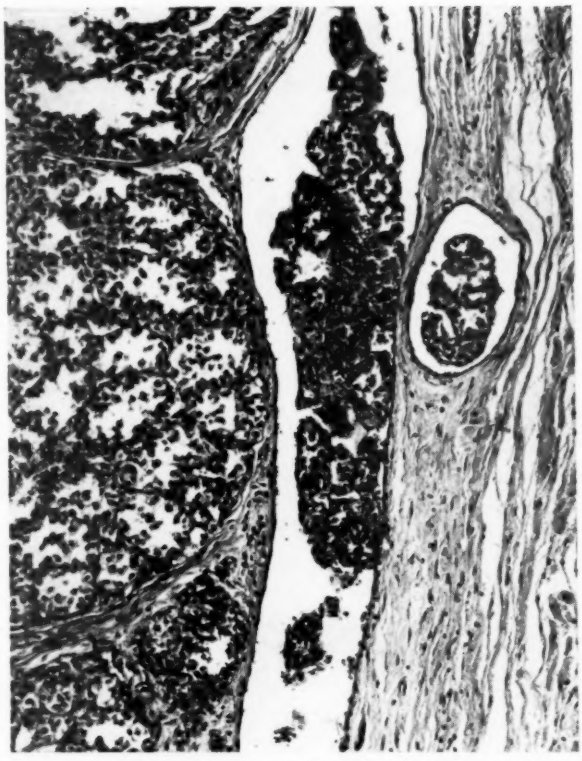

FIG. 6.—Venous invasion at periphery of primary tumour. Note pseudo-acinar structure in the left half of the field due to degeneration of central tumour cells. H. & E. × 85.

There seems little doubt, however, that this tumour is an entity whatever its tissue of origin. The histological pattern has been reproduced fairly uniformly in all the examples so far published. It appears to arise within or in close proximity to skeletal muscle, usually of the limbs, and affects mainly young adults or children. Many metastasize though they may appear histologically benign. Invasion of veins in the primary growth, as was demonstrated in this case, may indicate the future behaviour of these tumours.

Summary

A malignant tumour arising in the rectus femoris muscle of a young boy is described. It is considered to be a non-chromaffin paraganglioma.

We wish to thank the Photomicrography Department, University of Edinburgh, for the illustrations.

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GUMMA OF THE LIVER IN CONGENITAL SYPHILIS

BY

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Modern methods of serological testing for syphilis in pregnancy combined with highly efficient anti-syphilitic therapy should now be making congenital syphilis a relatively rare disease. In addition, past reports have frequently emphasized the ease with which gummata of the liver, and, indeed, elsewhere, may be misdiagnosed. In these circumstances unusual manifestations of this condition are more than ever likely to be missed, and for this reason we feel our recent experience with gumma of the liver should be described.

Case Report

W.G., a boy of 6 years, the only son of parents both aged 40 years living in a small market town, was sent to the Out-patient Department with the suggested diagnosis of leukaemia. His history was of vague ill-health for one year, beginning with an episode called by his parents 'the blues', consisting of a period of extreme sensitivity to cold, with shivering and a blue-black appearance of the face and legs during the winter weather. This was followed by episodes of loss of appetite, pallor and pain in the left side of the abdomen lasting three or four weeks, but apparently without fever and without vomiting.

On examination he was pale, lethargic and febrile. The main physical sign consisted of a striking enlargement of the liver, especially the left lobe. The edge was well defined, reaching half-way to the umbilicus, and its surface was nodular. There was no generalized lymphadenopathy and the spleen was not palpable. The provisional diagnosis was secondary neoplasm, involving the liver.

During his first few days in hospital he showed a sustained fever averaging 100° F. and had a persistently high E.S.R. to 100 mm. in one hour. The blood picture was as follows: Hb 73%, P.C.V. 35%, M.C.H.C. 31%, W.B.C. 7,000/c.mm. (polymorphs 47%, eosinophils 2%, lymphocytes 42%, abnormally large lymphocytes 5% and monocytes 7%).

Liver function was tested by zinc sulphate, thymol turbidity, thymol flocculation and cephalin cholesterol tests, which were all normal. The alkaline phosphatase was 27·5 units (Jenner and Kay) and the serum bilirubin was 0·3 mg./100 ml.

Mantoux testing (10 international units) was negative and *x*-ray examination of the chest, abdomen and long bones showed no abnormality.

At laparotomy the liver was found to be studded throughout with round greyish nodules with a large mass coalescing in the left lobe to cause the enlargement which constituted the presenting physical sign. Careful search of the abdomen did not reveal any primary neoplasm, but the findings were thought to bear out the original diagnosis.

Histology. The report, by Dr. J. Hart-Mercer, was as follows :

'There is no sign of neoplasm. The nodular lesion is essentially a necrotizing chronic granuloma with almost complete obliteration of the local parenchyma. Included in the specimen are surviving areas of liver tissue but these are also being invaded by the granulomatous process which is spreading here mainly by the lymphoreticular tissue of the larger portal tracts. With a picture of necrotic foci rather resembling caseation associated with epithelioid reaction and Langhans giant cells, tubercle has to be considered.'

Serological Tests. As the Mantoux test was again negative a Wassermann reaction was performed and found to be positive. Blood Wassermann tests were repeatedly strongly positive, but examination of the cerebrospinal fluid revealed no evidence of syphilis. The parents were then investigated and the mother was found to have latent spyhilis. She had a strongly positive blood Wassermann reaction but normal cerebrospinal fluid with a negative Wassermann reaction. There was no clinical evidence of syphilis. The father was entirely negative. Detailed review of the child revealed no other sighs of congenital syphilis, and, in particular, re-examination of radiographs of the long bones showed no evidence of osteoperiostitic changes.

Treatment. Treatment was initially with potassium iodide, starting with 1 grain daily and increasing rapidly up to 10 grains three times daily. To this was added bismuth metal suspension ('chlorostab' brand) beginning with 50 mg. weekly and increasing gradually until the patient was receiving 150 mg. per injection, which was given deeply intramuscularly in the upper outer quadrant of alternate buttocks.

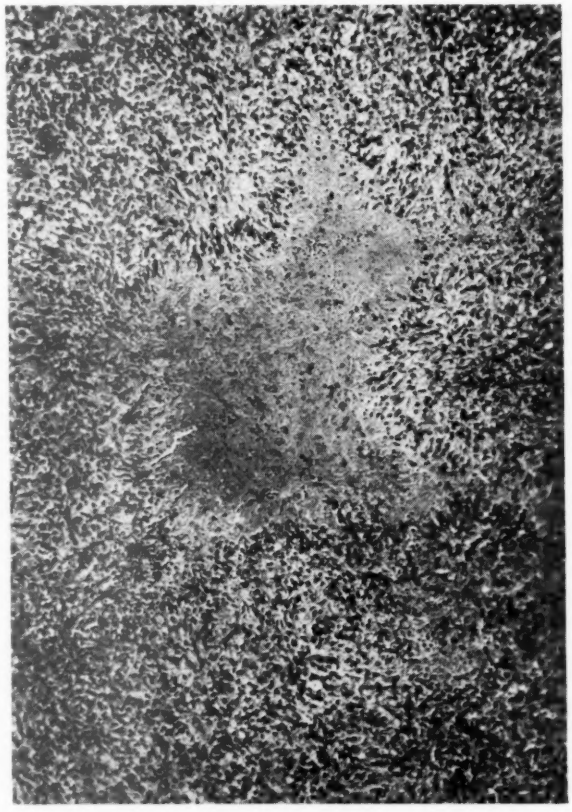

FIG. 1.—A small gummatous nodule in the liver. (× 90)

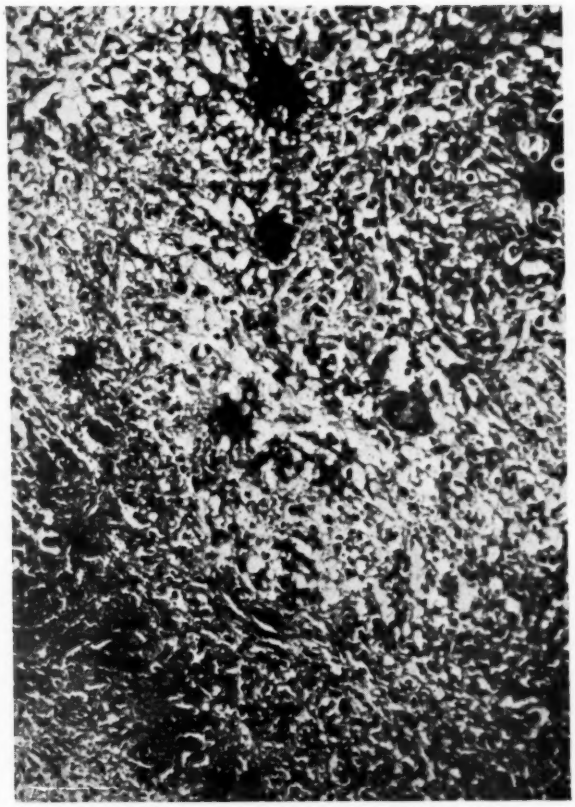

FIG. 2.—High-power view of liver showing multinucleate giant cells. (× 190)

An aqueous crystalline penicillin preparation was started on the tenth day after commencing treatment, beginning with 5,000 units six hourly and increasing to 50,000 units per injection in a further 10 days. After two weeks a delayed absorption product ('prolopen', Messrs. Glaxo Laboratories) was given once daily until a total of 6·3 mega units of penicillin had been administered.

After nearly three months, out-patient treatment was begun, consisting of 0·2 ml. bismuth weekly for 10-week periods alternating with 900,000 units penicillin per week for seven-week periods. A total of six courses of bismuth and 39 mega units of penicillin has been given to date.

Even the short pre-penicillin course produced a dramatic decrease in the size of the liver, and by the time penicillin was begun it had receded to only half an inch below the costal margin.

Liver function tests on discharge from hospital and repeated one year later were normal and the boy has now attained a negative serology for syphilis.

Comment

Nabarro (1954), with his very extensive experience of congenital syphilis, states that hepatic gummata are of great rarity in this variety of the disease. He says that the usual histological picture in the liver consists of a diffuse small cell infiltration occurring *in utero* and in the first months of life, succeeded later in some cases by fibrosis or cirrhosis varying from a microscopic lesion to complete destruction of the liver architecture. He quotes only two cases of gumma of the liver, described by Carpenter (1901) and Hutinel (1926), the former in an infant aged 8 months and the latter in a newborn infant, and says that he personally has not seen one.

McCrae and Caven (1926) reviewed 100 cases of tertiary syphilis of the liver, including five patients diagnosed as having congenital syphilis, aged 3, 13, 16, 18 and 19 years respectively. In the latter the liver was diffusely enlarged but the exact histology was unrecorded. Hahn (1943) examined 66 tertiary syphilic livers at necropsy in adults, and pointed out that in only nine was the true diagnosis made in life. Shapiro and Weiner (1951) described a further 79 necropsies, all in adults, and made the observation that 'the visceral manifestations of late syphilis through their rarity have been neglected'.

Flegel (1951) gave very detailed accounts of the livers in 22 children examined at necropsy at ages ranging from a stillborn infant to one aged 2½ years of age. All had syphilitic changes, but in very few had the liver architecture been replaced by granulation tissue, and in none was there a striking picture of naked-eye gummata, the liver being always enlarged but usually smooth. His account of the histology accords closely with that of Nabarro.

Jeans (1957) states that 'gummata may occur in almost any part of the body but they are rare in the liver, spleen and lungs'. He refers to one case he had seen which probably had gummata of the liver, but without any details.

Only one other reference to gumma of the liver, in an infant, was found in an article by Gerlóczy (1939), but this article could not be obtained. Isolated gummata of the pancreas (Raeburn, 1951), and the stomach (Willeford, Childers and Hepner, 1952) have also been recorded.

A recent report by Macfarlane, Johns and Schofield (1955) has emphasized these points. Their survey covered 200 patients with congenital syphilis of whom 172 (86%) were found to have late syphilis. Of these, 105 had ocular lesions, including interstitial keratitis, optic atrophy choroiditis and iridocyclitis. Twenty-five had evidence of neurosyphilis, including juvenile and general paresis, tabes dorsalis, eighth nerve deafness, epilepsy and mental changes. Bone changes were found in 11 patients and joint changes in 16.

Only two patients had gummata, a girl of 9 years with a gumma of the larynx, and a man aged 28 years with a gumma of the testis, which had been removed as a malignant tumour.

These reports serve to emphasize the rarity of gumma in the viscera, and particularly in the liver, in childhood, and also the difficulty which may arise in diagnosis at any age. The striking features in this child are that such a condition can develop so early and with no other signs of the disease, presenting, as in many adults with tertiary syphilis, signs imitating malignant disease.

Summary

The case is reported of a child aged 6 years presenting with an isolated picture of gummata of the liver.

Allowing for the rarity of gummatous hepatitis in children, the remarkable ability of this disease to masquerade as other conditions serves as a reminder that a serological test for syphilis before operation in similar cases is worthy of consideration.

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PAPER ELECTROPHORESIS OF SERUM PROTEINS IN CHILDREN

BY

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Since the description of paper electrophoresis in 1950 by Cremer and Tiselius and by Durrum among others, considerable interest has been shown in this cheap and relatively quick method of separating the various protein fractions. The serum proteins move through the fine cellulose mesh of the paper under the influence of an electric current, the separation of the various fractions being brought about by differences in their electrophoretic mobility at a selected *p*H. The bands are then shown up by staining with a protein dye. Usually five separate fractions are seen: albumin and four globulin fractions, designated α_1, α_2, β and γ (Fig. 1). The

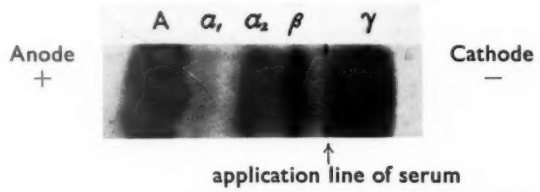

FIG. 1.—Paper electrophoresis slip showing the five serum protein fractions. Protein molecules are negatively charged at *p*H 8·6 and move towards the anode.

albumin fraction is more or less homogeneous, but the various globulin fractions are heterogeneous and can be further subdivided by the use of other physical methods or biological techniques. The protein fractions obtained by paper electrophoresis approximate closely to those obtained by the original Tiselius method of electrophoresis in free solution. It is technically difficult, however, to estimate the various proteins quantitatively by the paper method (Wolstenholme and Millar, 1956).

As we wished to study protein changes in large numbers of children we decided not to attempt elution or scanning of the strips and to accept a visual comparison with normal controls as adequate for our purpose. The technique described by Flynn and de Mayo (1951) was used with a few minor modifications. A slightly larger quantity of serum —namely, 0·02 ml.—than those authors used was applied to the paper from an accurately calibrated siliconed pipette, and we chose azocarmine B as the protein dye. When collecting blood samples by finger-prick care was taken to avoid haemolysing the specimen, because if free haemoglobin was present it appeared as a dense band in the $\alpha_2\beta$ region

The aim of the investigation was to study the value of the method in paediatric hospital practice. Several reports on electrophoretic pattern changes in adults have been published, including those of Flynn (1954) and Penman (1956), but only one dealing specifically with sick children has come to our notice, that of Corbeel (1954), and his results were not very detailed.

Normal Patterns

To establish the normal pattern from birth to 12 years of age 130 paper strips were prepared from children without physical disease who attended the out-patient department. Average strips and those representing the extreme limits of normal for each year of age were mounted on cards and used as controls in the study of diseases. Bands which were outside the range of normal for the relevant age were interpreted as showing an increased or decreased intensity. The variations with age proved to be more or less identical with those described by Knapp and Routh (1949) using the classical Tiselius method. The most striking change is in the γ globulin, which at birth is at the adult level, but falls rapidly in the next three or four months until it almost disappears, only a faint stain being visible on the strip. Thereafter it gradually increases, but is still low at 1 year. By 2 years it has increased considerably, and between 6 and 10 years the adult level is again reached. The α_2 globulin band is well marked in the infant and gradually decreases to the adult level by about 12 years of age

The albumin and α_1 and β globulin bands do not alter significantly with age (Fig. 2).

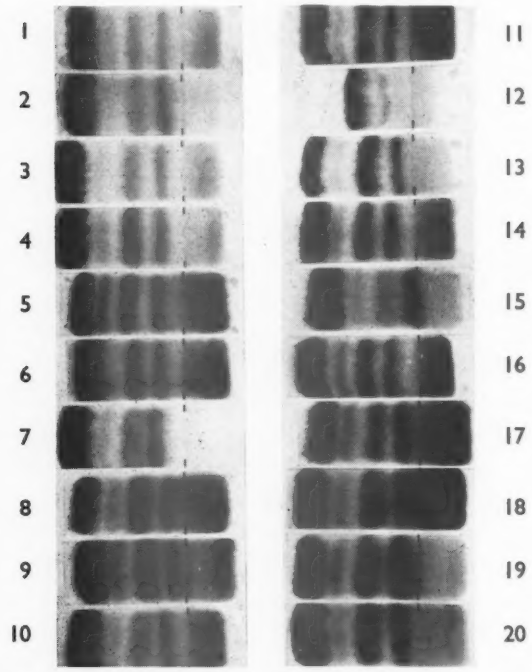

FIG. 2.—Normal serum protein electrophoretic patterns (Nos. 1-3) and those of various diseases (Nos. 4-20). Details are given in the table below.

abnormal. Early in the course of the disease the α_1 and α_2 globulin bands were increased, and later on the γ globulin became increased unless the infection had been very rapidly overcome. Out of 23 examples of acute infection, such as streptococcal tonsillitis, lobar pneumonia or bronchopneumonia, gastro-enteritis and staphylococcal osteomyelitis, there were only two normal strips; 11 showed α_1 and α_2 globulin increases, and 10 a γ globulin increase as well. This type of response was seen also in eight out of nine infants under 1 year with acute infections. The γ globulin, normally low in this period, was capable of increasing in response to infection. Once the infection was overcome the protein patterns reverted to normal.

In subacute infections it was usual to find an increase in α_2 and γ globulins—for example, in active bronchiectasis or in fibrocystic disease of the pancreas or ulcerative colitis. Of 22 cases of fibrocystic disease, nine showed α_2 and γ globulin increases and seven showed γ globulin increases only; five were normal and one had a low γ globulin. Of eight cases of ulcerative colitis, five showed α_2 and γ globulin increases and three showed γ globulin increases only. Two early cases showed α_1 and α_2 globulin increases only. In three cases of Caffey's disease (infantile cortical hyperostosis) α_2 and and γ globulin increases occurred which after several months returned to normal. This suggests that there is an inflammatory basis to Caffey's disease.

In chronic infections the γ globulin only was raised, for example, in six cases of chronic tuberculosis.

The serum of seven out of 14 children with a history of constantly recurring infections showed

KEY TO SERUM PAPER ELECTROPHORETIC PATTERNS IN FIG. 2

Number	Sex	Age	Disease	Pattern Changes				
				A	α_1	α_2	β	γ
1	M	1 day	Normal					
2	M	4 mos.	Normal					
3	F	20 mos.	Normal					
4	M	7 yrs.	Acute tonsillitis		+	+		
5	F	5 yrs.	Fibrocystic disease		+	+		+
6	F	3 yrs.	Chronic pulmonary tuberculosis					+
7	M	2 yrs.	Agammaglobulinaemia					−
8	F	10 yrs.	Acute rheumatic fever		+	+		+
9	M	2 yrs.	Still's disease		+	+		+
10	M	12 yrs.	Rheumatoid arthritis					+
11	M	4 yrs.	Acute nephritis			+		+
12	M	4 yrs.	Nephrotic syndrome	−		+	+	−
13	M	4 yrs.	Nephrotic syndrome during treatment			+		−
14	M	7 yrs.	Infective hepatitis			+		+
15	M	2 mos.	Neonatal hepatitis			−		
16	F	10 mos.	Congenital obliteration of bile ducts		+			+
17	M	10 yrs.	Cirrhosis					+
18	F	8 yrs.	Haemosiderosis					γ_1+ γ_2+
19	F	16 mos.	Liver disease with hypercholesterolaemia			+	+	
20	F	8 mos.	Idiopathic hypercalcaemia of infants			+	+	

Abnormal Patterns

Infections. No change in electrophoretic pattern was detected in mild infections such as colds, bronchitis or low-grade urinary infections. However, where fever, leucocytosis and constitutional disturbance were present the proteins were usually

TABLE 1

COMPARISON OF SERUM PROTEIN ELECTROPHORESIS FINDINGS IN RHEUMATIC FEVER, STILL'S DISEASE, RHEUMATOID ARTHRITIS AND ACUTE NEPHRITIS

Condition	Total Number of Cases	α_1, α_2 and γ Globulin Raised	α_2 and γ Globulin Raised	γ Globulin Raised	Normal Pattern
Rheumatic fever	20	5	4	7	4
Still's disease	8	6	1	1	0
Rheumatoid arthritis	7	0	2	2	2
Average E.S.R. (mm./1 hr.)	—	51	44	35	13
Range of E.S.R. (mm./1 hr.)	—	11–80	12–112	6–95	6–24
Acute nephritis*	32	0	12	3	12

* In three cases γ globulin was low; in two α_2 globulin only was raised.

normal protein patterns, while in three cases there were α_2 and γ globulin increases of the order already noted in acute and chronic infections. Two showed a low γ globulin, a condition one might term 'hypogammaglobulinaemia'; in the remaining two no γ globulin at all was visible on the strip. In these cases the diagnosis of 'agammaglobulinaemia' was confirmed by the classical Tiselius technique, as the γ globulin concentration was less than 0·1 g. per 100 ml. It is of considerable interest that in a third case of agammaglobulinaemia there was no history of recurrent infections and the child was examined by us because he had rheumatoid arthritis (a condition which we were studying at the time) with typical bilateral involvement of knees and ankles. The association of rheumatoid arthritis with agammaglobulinaemia is unexpected in view of the hypogenesis of reticulo-endothelial tissue associated with the latter condition.

Very high γ globulin levels were found in three children with severe chronic staphylococcal infections, two with empyema and one with enteritis. Janeway, Craig, Davidson, Downey, Gitlin and Sullivan (1954) described this condition in a group of infants, calling it 'hypergammaglobulinaemia' as the γ globulin level was higher than that seen in the usual chronic infection. The titre of antibodies was high in their cases, so that the failure to overcome the infection speedily lay elsewhere than in the immunity mechanism.

Rheumatic Fever, Still's Disease and Rheumatoid Arthritis. The rheumatic diseases were selected for study because a rise in total globulin commonly occurs in these conditions, but it soon became apparent that the globulin patterns were in no sense diagnostic and resembled closely those seen in subacute and chronic infections. When tests were made within a day or two of the onset of rheumatic symptoms the γ globulin level was always raised, a finding which was helpful on one occasion in differentiating acute osteomyelitis from rheumatic fever, as the γ globulin level is not raised in the early stages of acute osteomyelitis. Twenty children with rheumatic fever were studied, eight with Still's disease (joint swellings, adenopathy and splenomegaly, with or without rash or pericarditis) and seven with rheumatoid arthritis (arthritis being the only clinical manifestation of disease). The results obtained when the children were first seen are shown in Table 1. A rise of α_1, α_2 and γ globulins occurred in the most acute cases of rheumatic fever, three of which had pericarditis, and in children with the widespread tissue involvement of Still's disease. Changes in α_2 and γ globulins, or γ globulin increases alone, were found in the less acute cases of rheumatoid arthritis and in the later stages of rheumatic fever and Still's disease. With clinical improvement the α_2 globulin fell to normal before the γ globulin. Children showing normal patterns were, without exception, very mildly affected or had passed the acute phase of illness before coming to hospital.

As with simple infections, the more acute cases tended to have higher erythrocyte sedimentation rates (E.S.R.). Great variation, however, occurred and, although the average E.S.R., as seen in the table, worked out in descending order as the cases decreased in acuteness, the range of E.S.R. was almost the same in each group with abnormal globulins. In assessing the stage and severity of rheumatic fever, Still's disease and rheumatoid arthritis, therefore, it may be an advantage to take the electrophoretic findings as well as the E.S.R. into consideration. This may be particularly useful in cases with cardiac failure.

When followed throughout the course of these disorders the E.S.R. and electrophoretic pattern did not run parallel (Table 2). The tests were performed weekly on the same blood sample. Out of nine cases of rheumatic fever thus followed, four showed abnormal electrophoretic patterns for weeks or even months after the return of the E.S.R. to 10 mm. in one hour or less. In two cases, on the other hand,

TABLE 2

RELATION BETWEEN RETURN TO NORMAL OF SERUM PROTEIN ELECTROPHORESIS PATTERN (S.P.E.) AND E.S.R.

Conditions	Total Number of Cases	S.P.E. and E.S.R. Normal Together	S.P.E. Normal before E.S.R.	E.S.R. Normal before S.P.E.
Rheumatic fever ..	9	3	2	4
Still's disease and rheumatoid arthritis	6	5	1	0
Acute nephritis ..	10	4	6	0

the electrophoretic pattern became normal before the E.S.R., and in three the tests corresponded exactly. So few cases of rheumatoid arthritis had returned to normal at the time of assessment that the numbers are too small to be of much value.

To summarize, the changes in serum protein electrophoretic pattern which may be found in rheumatic fever, Still's disease and rheumatoid arthritis are of no help diagnostically and closely resemble those seen in simple infections. Electrophoresis may, however, be a useful adjunct to determination of the E.S.R. in assessing the stage and severity of the disorder and in deciding how long to continue treatment, whether by cortisone, salicylates or bed rest.

Acute Nephritis. In view of the aetiological similarity between acute nephritis and the rheumatic conditions, it was of interest to find how closely the patterns resembled each other in the two groups. The study covered 32 children with acute nephritis (see Table 1). None showed the α_1, α_2 and γ globulin increases seen in the most acute rheumatic conditions; 12 showed an α_2 and γ globulin rise, two an α_2 globulin rise only, while in three there was a slight increase and in three a slight decrease in γ globulin. Twelve showed a normal pattern, but nine of these children had passed the most acute phase when first seen. Consecutive studies (Table 2) showed that in four out of 10 cases the E.S.R. and serum protein electrophoretic pattern returned to normal together, while in six cases the electrophoretic pattern returned to normal first. Usually, but not invariably, the albumin disappeared from the urine before the results of blood tests became normal.

Of five cases of chronic nephritis of long standing with uraemia, four showed a slight reduction of γ globulin.

Nephrotic Syndrome. Changes in serum proteins in the nephrotic syndrome are dramatic and well recognized, the fall in γ globulin being in contrast to the rise seen in the acute stage of nephritis. The electrophoretic pattern is diagnostic with a low albumin, an $\alpha_2\beta$ complex, the two bands having been replaced by one broad deeply staining band, and a low γ globulin; the latter disappears in the most severe cases to give an acquired agammaglobulinaemia. In milder cases a pattern which might be termed 'partially nephrotic' occurs: the albumin is slightly reduced, the α_2 band is broader and more densely stained than normal, and the γ globulin is reduced. This partial pattern, which we first recognized in nephrotic patients improving under hormone therapy, was of value in assessing the cause of symptomless albuminuria in three cases. These children gave no history of oedema and had no urinary infection, their albuminuria being discovered on routine testing. In two the serum cholesterol was raised. None showed a reversal of albumin:globulin ratio, as the rise in α_2 globulin was offset by the fall in γ globulin. In each case the blood urea and an intravenous pyelogram were normal. One progressed to classical nephrosis, but in the other two the electrophoretic patterns returned to normal with disappearance of the albuminuria without treatment, and these children might be considered to have suffered *formes frustes* of the nephrotic syndrome. When stains for lipid or cholesterol are used, increased amounts of both fat and cholesterol are seen in the $\alpha_2\beta$ region.

In 25 cases of nephrosis a serial study of the pattern changes during hormone therapy was made. At the time of the disappearance of albuminuria the pattern began to alter. The $\alpha_2\beta$ complex separated into α_2 and β bands; later on the albumin re-formed, and finally after several weeks the γ globulin returned to normal. The serum cholesterol level fell to normal at about the same time as the γ globulin regenerated. The final return of the γ globulin to normal was used in determining the duration of full hormone therapy; the periods of treatment required to achieve it varied from case to case and did not always correspond with the apparent initial severity. With other forms of treatment, such as with resins, urea or mercurial diuretics, resulting in loss of oedema, but not to disappearance of albuminuria, no improvement in the nephrotic pattern was seen. When relapse occurred the first abnormality noted was the reappearance of albuminuria, and only after a week or so did the serum protein picture alter. This is consistent with present concepts of serum protein synthesis and storage.

Liver Disease. Alteration in serum proteins is the basis of the turbidity tests—for example, the thymol turbidity, Takata-Ara and Kunkel tests, the last being largely dependent on an increase in

TABLE 3

SERUM PROTEIN ELECTROPHORESIS CHANGES IN CERTAIN LIVER DISEASES

Disease	Total Number of Cases	α_1 Globulin		α_2 Globulin		β Globulin		γ Globulin		Normal Pattern
		−	+	−	+	−	+	−	+	
Infective hepatitis	21	0	0	2	3	1	1	0	3	14
Neonatal hepatitis	7	0	0	2	0	2	0	0	0	4
Congenital obliteration of bile ducts	8	0	4	0	0	0	0	0	3	3
Cirrhosis	15	0	0	5	0	0	0	0	11	2

γ globulin. In infancy these tests are notoriously unreliable, and this may be because of the difference in globulin pattern normally seen at this age, particularly the low γ globulin. By comparing the electrophoretic patterns of jaundiced babies with those of normal infants it was hoped that more valuable information might be obtained than from the turbidity tests alone. However, the results, although useful in some cases, were by no means uniform.

Of 21 cases of infective hepatitis in childhood (Table 3), 14 showed normal strips, three a rise in α_2 and β globulins, two a reduction in α_2 globulin, one a raised β globulin and one a lowered β globulin. From seven cases of neonatal hepatitis, four strips were normal, one showed a low $\alpha_2\beta$, one a low α_2 and one a low β globulin. Of eight cases of congenital obliteration of the bile ducts, proved at operation or necropsy, three showed normal strips, three an increase in α_1 and γ globulins, and one an increase in α_1 globulin only; the other showed variable changes in α_2 and β globulins. In 15 cases of cirrhosis only two strips were normal, and 11 showed a rise in γ globulin. Of these, two cases of haemosiderosis showed a dense band filling in the space between the β and γ globulins, an increase in the so-called γ_1 globulin. In four cases the α_2 globulin was low in association with a raised γ globulin, and in one the α_2 globulin was low with a normal γ globulin. Of 16 cases diagnosed incompletely as 'hepatosplenomegaly', 12 were normal. In three the α_2 globulin was low and the γ globulin raised, a pattern seen in cirrhosis of the liver. In one interesting case of galactosaemia in an infant the depression of α_2 and β globulins seen on the strip reverted to normal a week after the introduction of a lactose-free diet. In two cases of hepatic coma the α_2 and β globulins were low and the γ globulin high. Two rather unusual cases with jaundice and hypercholesterolaemia in which no liver biopsy was performed showed marked α_2 and β globulin increases.

In reviewing the changes in liver disease certain general patterns were apparent. The α_1 globulin was increased only in congenital obliteration of the bile ducts, and the α_2 globulin only in infective hepatitis. A decrease in α_2 globulin was a fairly common finding and was seen in other cases of infective hepatitis, in neonatal hepatitis and in cirrhosis. Changes in β globulin were rare and variable. A rise in γ globulin was almost the rule in cirrhosis, and occurred occasionally in infective hepatitis and in congenital obliteration of the bile ducts.

Idiopathic Hypercalcaemia of Infants. A study was made of 18 infants with idiopathic hypercalcaemia, but 10 of them had already passed the acute phase. In eight the serum calcium level was still raised, and in four of these there was a very definite increase in α_2 and β globulins, similar to the pattern seen in the two cases of liver disease with hypercholesterolaemia mentioned above. Two strips were also stained for fat and showed a rise in β lipoprotein concentration. One infant showed a rise in α_2 and γ globulins, and one a rise of γ globulin only. The other two infants with an increased blood calcium had a normal pattern. Two of the 10 infants with a normal serum calcium level by the time of examination showed abnormalities in the α_2 and β band persisting beyond the hypercalcaemic phase—a finding of some interest.

Miscellaneous Conditions. Strips were prepared from nearly 200 children in hospital, but no changes of diagnostic value were found. Conditions investigated included, among many others, the following: malignant tumours, leukaemia, Hodgkin's disease, haemolytic anaemia, histiocytosis, Gaucher's disease, thyrotoxicosis, cretinism, coeliac disease and pink disease.

Discussion

Five serum protein bands have been studied by paper electrophoresis. The albumin band is homogeneous or nearly so, but the other bands are mixtures of several proteins (Table 4). It will be seen that many specific proteins have been isolated from these fractions, although the α_2 globulin band is still largely unidentified. Some proteins are

TABLE 4

PROTEIN COMPONENTS OF PLASMA (ADAPTED FROM HUGHES, 1954)

Electrophoretic Band	Known Components	Concentration in Plasma (g./100 ml.)
Albumin	Crystalline albumins	4·30
α_1 Globulin ..		0·30
	α_1 Mucoprotein	0·05
	α_1 Lipoprotein	0·20
α_2 Globulin ..		0·70
	Ceruloplasmin	0·03
	α_2Lipoprotein	0·02
	Complement	—
β Globulin		1·10
	Transferrin	0·25
	β Lipoprotein	0·40
γ_1 Globulin		0·50
	Fibrinogen	0·30
	Antihaemophilic globulin	—
	Isohaemagglutinins	—
γ Globulin or γ_2 Globulin		0·90
	Diphtheria antitoxin	0·001
Total plasma protein	.. .. ..	7·80

TABLE 5

DISEASES WHICH MAY BE ASSOCIATED WITH GLOBULIN CHANGES

Globulin	Decreased	Increased
α_1	None	Acute infections Rheumatic fever Still's disease Congenital obliteration of bile ducts
α_2	Infective hepatitis Neonatal hepatitis Cirrhosis Galactosaemia	Acute infections Subacute infections Rheumatic fever Still's disease Rheumatoid arthritis Acute nephritis Nephrotic syndrome Infective hepatitis Liver disease with hypercholesterolaemia Idiopathic hypercalcaemia of infants
β	Infective hepatitis Neonatal hepatitis Galactosaemia Hepatic coma	Nephrotic syndrome Infective hepatitis Liver disease with hypercholesterolaemia Idiopathic hypercalcaemia of infants
γ	Hypogammaglobulinaemia Agammaglobulinaemia Chronic nephritis with uraemia Nephrotic syndrome	Subacute infections Chronic infections Rheumatic fever Still's disease Rheumatoid arthritis Acute nephritis Infective hepatitis Congenital obliteration of bile ducts Cirrhosis Hepatic coma

present in such low concentration that they are not likely to contribute much to the fairly gross quantitative levels required for visual appreciation; for example, it would appear that the increase in γ globulin found in chronic infections is greater than could be accounted for by a rise in specific antibodies, as they form such an infinitesimal part of the γ globulin total. The function of the apparently inert proteins in the various fractions is unknown, and their presence may be masking changes of specific active proteins occurring in disease. With the further identification of serum proteins diagnostic changes may be discovered which are not revealed by the present rather crude methods. To date only nephrosis, agammaglobulinaemia and multiple myeloma have pathognomonic patterns. The changes in infections, rheumatic conditions and liver disease may occasionally be of help in diagnosis, but, on the whole, their chief value lies in following the return to normal during the course of treatment.

The disorders which may be associated with an increase or decrease in the various globulin bands are shown in Table 5. Consideration of these may help to clarify the interpretation of the protein changes found in disease in childhood.

Summary

The normal serum protein patterns obtained by paper electrophoresis in childhood have been described. Assessment of abnormal paper strips by visual comparison with the range of normal for the age was considered adequate for clinical purposes.

Changes occurring in a variety of conditions, including simple infections, rheumatic affections, acute nephritis, nephrosis, liver disease, and idiopathic hypercalcaemia, have been discussed.

The method of paper electrophoresis has only limited diagnostic value, but it may provide a useful additional guide to progress in the rheumatic conditions, nephrosis and diseases of the liver in particular.

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A CLINICAL AND HAEMODYNAMIC STUDY OF VENTRICULAR SEPTAL DEFECT IN INFANTS

BY

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The concept of ventricular septal defect as a disease of little severity (Roger, 1879; Brown, 1950), has been upset by the observations of Marquis (1950) and Engle (1954). The median age at death in Abbott's (1951) cases was 14½ years; however, in common with others, we have observed severe disability and death in many younger children.

The advent of surgical therapy for this defect (Lillehei, Cohen, Warden, Ziegler and Varco, 1955), and the desirability of correction at an early age make it worth while to review the clinical features in the earliest age group. The haemodynamic findings will be given in some detail.

Material and Methods

Sixteen cases of ventricular septal defect occurring in infants aged 1 year or less were studied in 1955. Table 1 shows the age at onset of symptoms and examination. Special studies were undertaken because of significant disease, and a large percentage thus observed was less than 6 months of age. Cardiac catheterization was done in the usual fashion using the Waters-Conley cuvette oximeter for oxygen saturation assessment. Its accuracy was checked by two or more Van Slyke specimens. Expired air was collected in a Tissot spirometer and analysed for oxygen and carbon dioxide content by the Scholander method. Calculations of shunts and resistances were by the usual formulae.

The catheter was normally placed in the femoral vein after the infant had received light basal (barbiturate) anaesthesia. Procaine (1%) was used as a local supplement. Two patients who had suffered congestive failure received oxygen throughout the catheterization, as it was felt that arrhythmias were less frequent in this circumstance. Difficulty was found in recording adequate pulmonary capillary pressures. We have found this also in adults with a large left-to-right shunt where more advantageous circumstances exist. The femoral vein was routinely ligated. No death or complication attributable to catheterization occurred.

Clinical Features

The Symptoms. These (Table 2) are surprisingly constant, and compare well with those found in other severe left-to-right shunts. They consist principally in failure of growth, refusal to feed. frequent respiratory infections and a 'murmur',

TABLE 2

CLINICAL HISTORY IN 16 CASES

	Number	Percentage
Presenting Complaints		
Cough and respiratory infections	10	62
Failure of growth	9	56
Dyspnoea	3	19
'Murmur'	3	19
Easy fatiguability	2	12·5
Cyanosis	1	6
Rapid heart	1	6
All Complaints		
Cough and respiratory infections	13	81
'Murmur'	13	81
Feeding difficulties	9	56
Failure of growth	9	56
Excessive sweating	7	44
Dyspnoea	5	31
'Rapid heart'	2	12·5
Easy fatiguability	2	12·5
Cyanosis	2	12·5
Slow motor progress	1	6
Pallor	1	6
Hoarseness	1	6

TABLE 1

DISTRIBUTION OF PATIENTS ACCORDING TO ONSET OF SYMPTOMS AND AGE AT CATHETERIZATION

	Birth to 1 Month	2–3 Months	4–5 Months	5–7 Months	8–9 Months	10–12 Months
Age at onset of symptoms	4	5	4	–	3	–
Age seen and catheterized	2*	1	2	2	4	4

* Not catheterized until 2 months of age.

This latter was only rarely noted by the parents themselves. The early onset (Table 1) is noteworthy in some of the cases. Cyanosis—a rare feature in most adult series—occurred in some children. Excessive sweating in the absence of overt infections was not unusual. This has, however, been observed by us in other types of congenital heart disease. Lassitude—so commonly noted by the paediatrician—was seldom remarked upon by the parents. In a few cases the thrill was obvious to the family. Epistaxes, though common in older children with this defect, were absent in the patients studied.

The Signs. The most remarkable sign (Table 3) is growth failure; it occurs in most infants whose

TABLE 3
PRINCIPAL SIGNS

	Number	Percentage
Systolic murmur	16	100
Systolic thrill	13	81
Chest deformity	13	81
Cardiomegaly (clinical)	13	81
Right ventricular apex type	11	69
Anaemia (excluding physiological)	7	44
Dyspnoea (exertional)	7	44
Associated defects (3 herniae, 2 telangiectases)	5	31
Dyspnoea (at rest)	4	25
Triple rhythm	4	25
Congestive failure	3	19
Cyanosis (At rest)	2	12·5
Cyanosis (Exertional)		
Split pulmonic second sound	2	12·5
Pulmonary thrust	1	6
Recurrent laryngeal palsy	1	6

parents seek medical advice. Table 4 expresses this phenomenon in terms of growth percentile. It is seen that weight deficit is greater than height deficit though this latter is considerable. Head and chest size also tend to fall in the lower percentiles.

Further inspection often reveals Harrison's grooves (Fig. 1); these seem to be associated with dyspnoea or frequent respiratory infections. Breathlessness at rest is variable; this symptom occurs more often on exercise—usually crying and defaecation. Two cases showed cyanosis. Minor associated defects were found in five infants. The severe nature of the lesion is illustrated by the onset of congestive cardiac failure in three children. In two this responded adequately to therapy. Cough was by far the commonest sign in some of the infants; usually unassociated with cardiac failure, it may be subsequent to a change in the pulmonary blood flow.

Cardiovascular examination gave a constant picture. Enlargement of the heart was usual, as this was one of the criteria for further study. The apical impulse was frequently of the right ventricular type. A gallop rhythm was occasionally palpated inside the displaced apex. A systolic thrill was felt over the lower left interspaces. It was coarse and widespread, corresponding well to Roger's original description. The thrill, however, may not appear for several months after birth. We have had the opportunity to observe two patients from birth, in whom no thrill could be felt until 3 and 4 months of age respectively. Similar findings have been observed in some cases of Fallot's tetralogy (Maxwell, 1954).

The character of the second sound at the pulmonary area is of some interest. It has been observed by Leatham (1952) that a widely split second sound is common in left-to-right shunts, usually in association with electrocardiographic evidence of right bundle branch block. Wood (1950) noted this sign in older patients with ventricular septal defect. This elegant clue was seldom found in the infant group studied here. Generally auscultation reveals a single sound, as in normal infants. Again, pathological intensity of this sound has not been observed, an expected finding in view of the wide range in normals of this age.

Apical diastolic murmurs were not heard in this group, which contrasts with Wood's (1950) findings for older patients with the same defect.

Anaemia is not uncommon. An attempt was made to exclude the 'physiological' anaemia of infancy in assessing the figures, and there is some

FIG. 1.—Note the Harrison's grooves.

evidence that a true iron-deficiency state exists. Certainly difficulty is found in introducing a mixed, iron-containing diet to these infants, and a staple diet of cow's milk is usually deficient in this element. The frequent infections introduce another need for iron (Wintrobe, 1951) and aggravate the condition.

These infants are lethargic and inactive. Muscular hypotonia is not unusual and this combination results in failure to pass the milestones of motor development at the proper time. Thus the ages of rolling over, sitting up and crawling may be delayed. Observation of other older cases suggests that those who live may catch up in the second and third years.

The single case of laryngeal palsy is not very unusual, though it is perhaps more common in cases of atrial septal defect.

Discussion of Clinical Features

The history is that of any severe left-to-right shunt, resembling most closely that of a 'malignant' patent ductus. Like the latter, the symptoms may exist from the perinatal period and are characterized by feeding problems, failure of growth, respiratory infections and a murmur. This latter corresponds with the description given for older children and adults. The thrill, however, may not appear until some months have elapsed. The murmur and thrill may be confused with that of aortic or subaortic stenosis; we have encountered four such cases in the period of this study. In these the murmur and thrill were not distinguishable from those of ventricular septal defect. However, good growth and lack of cardiomegaly and pulmonary plethora were useful differential points. They are more difficult to tell from cases of ventricular septal defects without pulmonary hypertension. A similar difficulty was reported by Taussig (1955). Brachial arterial tracing may be a useful distinguishing point.

Radiology

As a result of selection, enlargement of the heart was usual. Biventricular increase was common, and differentiation of the major chamber enlargement was difficult in these circumstances. The pulmonary arc was prominent, and the lung fields engorged: relative peripheral hypovascularity was seen in several patients, reflecting perhaps the situation reported by Hultgren, Selzer, Purdy, Holman and Gerbode (1953), in cases of patent ductus with pulmonary hypertension. The linear markings of Kerley (1951) were not seen. This was not unexpected, as this sign is related to the level of the pulmonary capillary pressure and not to the pulmonary arterial tension (Bruwer, Ellis, and Kirklin, 1955).

A corollary to increased pulmonary blood-flow is increased left atrial size. This has been said (Keats and Steinbach, 1955) to be characteristic of patent ductus. However, the left atrium may be prominent in any condition with pulmonary plethora and intact atrial septum. Brostoff and Rodbard (1956) have demonstrated the hydrodynamic cause in simulated ventricular septal defect.

Common radiological findings are illustrated in Figs. 2, 3, 4 and 5.

It will be seen that the findings in severe ventricular septal defect are very similar to those reported in 'malignant' patent ductus by Adams, LaBree and Stauffer (1950); it is probable that many cases are radiologically indistinguishable by ordinary techniques. While hypervascularity and right ventricular enlargement will occur in some cases of atrial septal defect, we have not noted left atrial enlargement in this condition. This is perhaps a useful differential point.

Routine angiocardiography has been of little value in delineating this lesion, and has only occasionally been employed by us. The size of the right ventricle and pulmonary arteries may sometimes be shown by this method, and the left ventricular dimension assessed by difference.

Electrocardiography

Most cases showed a right bundle branch block, often of the complicated type associated with increase in the right ventricular work (Wasserburger, 1956). Some cases may also show evidence of delay in activation time over the left ventricle in addition to the previous finding.

However, the electrocardiogram of ventricular septal defect is by no means unique; similar patterns may be found in patent ductus, again with signs of right and left ventricular overloading. The haemodynamic coincidence of these two lesions render this a reasonable finding. A common E.C.G. pattern is seen in Fig. 6.

Cardiac Catheterization

A. Diagnosis. The primary reason for the studies was confirmation and quantitation of the clinical diagnosis, and this was readily done in most cases. The increase in oxygen content from atrium to ventricle averaged 2·5 vol. in those studied while breathing room air. One case (No. 3 in Table 4) required 100% oxygen before the level of shunt was apparent. This was because of the extraordinayr degree of unsaturation present. Table 5 illustrates this point comparatively. In no case did we require to give adrenalin to show the level of shunt as has been suggested by Condorelli (Turchetti, 1954).

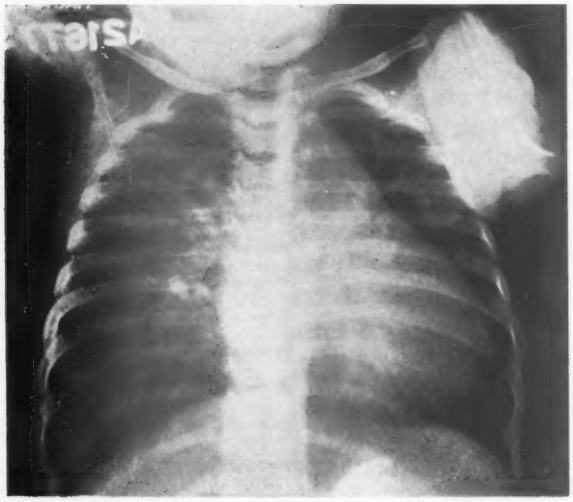


FIG. 2.—In this postero-anterior view there is cardiac enlargement, pulmonary plethora and prominence of the pulmonary arc.

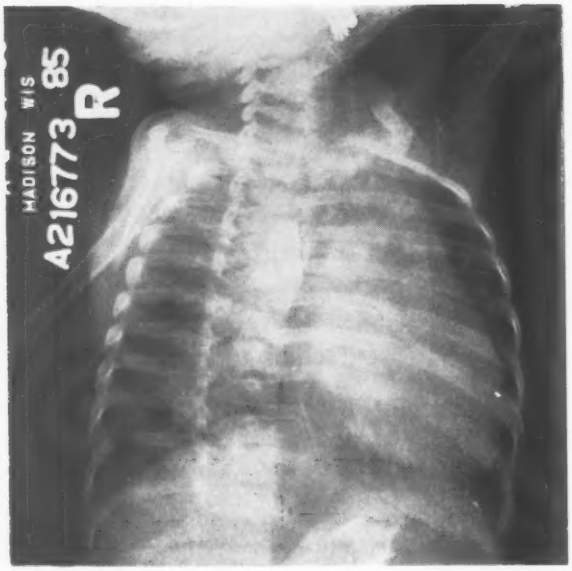


FIG. 3.—This R.A.O. view shows the right ventricular enlargement.

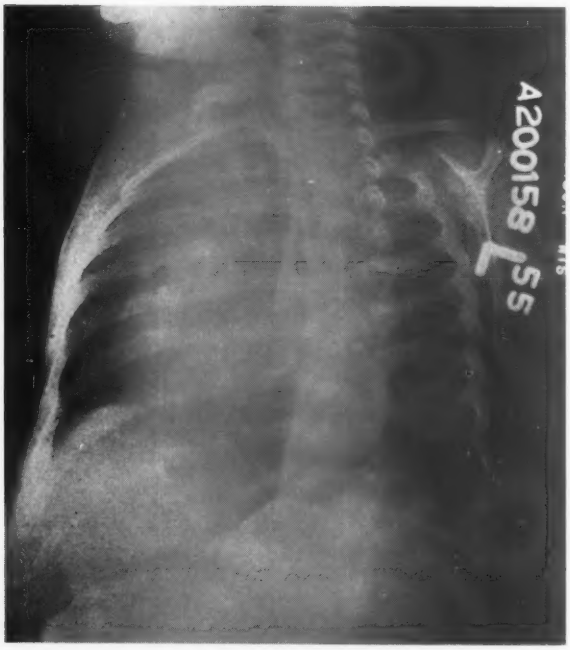


FIG. 4.—Note the enlarged left ventricle in this L.A.O. view.

FIG. 5.—The left atrium has displaced the oesophagus in this right oblique view.

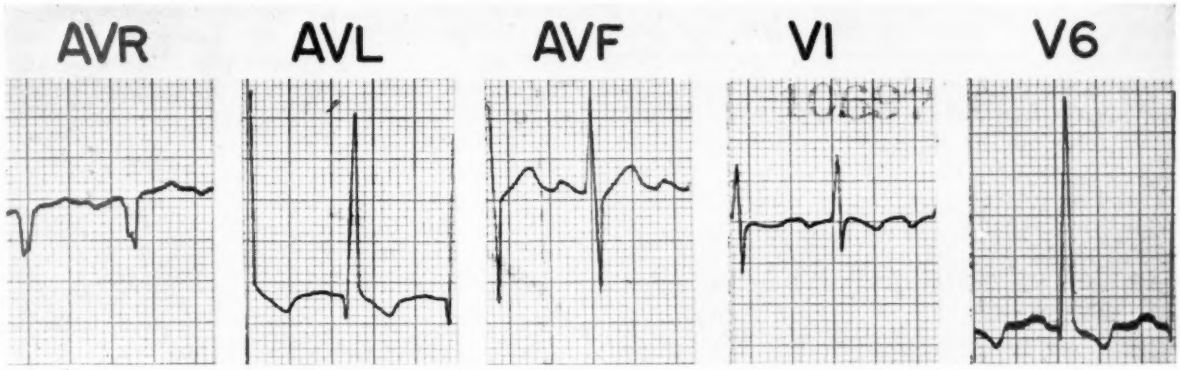


FIG. 6.—The E.C.G. of a case of ventricular septal defect aged 7 months. There is a delay in ventricular activation time over the left ventricle, *i.e.*, V.A.T. = 0·035-0·040 sec.

In some cases the left atrium was entered by way of a foramen ovale; that this was not a functioning defect was suggested by the lack of arterialization of the right atrium, and full saturation of the left atrium as compared with the pulmonary veins. The left ventricle was occasionally explored by this route also. In this age group, the technical problem of moving the catheter within the pulmonary circuit makes the exclusion of a patent ductus difficult*

* In one case since operated upon, a functioning patent ductus was found.

TABLE 5

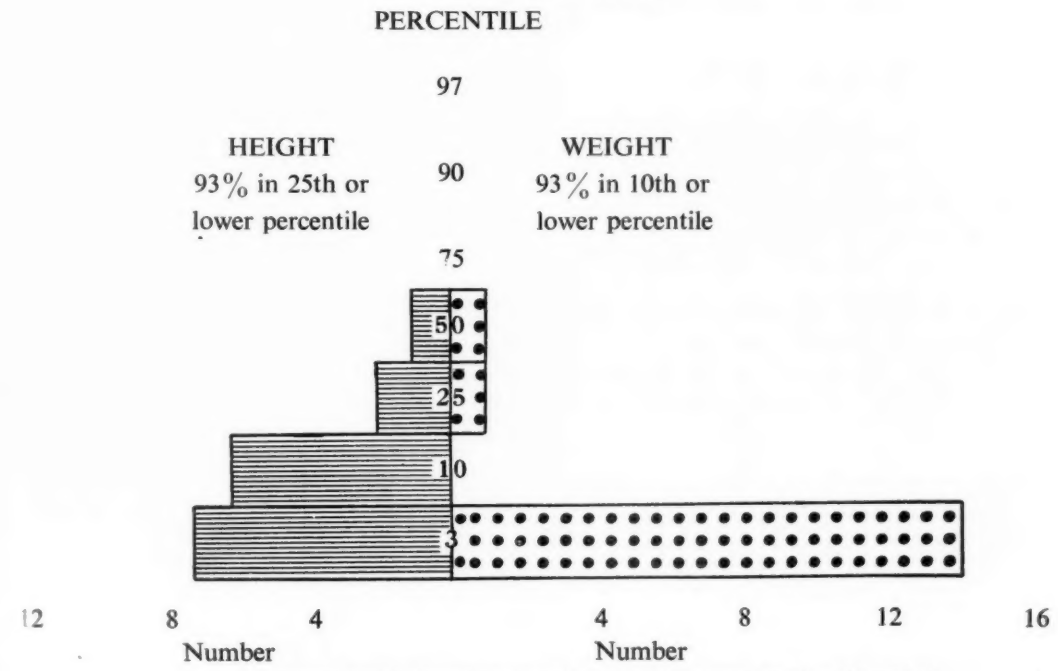
SATURATION LEVELS IN CASE 3 BREATHING AIR AND OXYGEN

Site	O_2 Saturation %	
	Air	100% Oxygen
Superior vena cava	22	72
Mid right atrium	23	77
Low right ventricle	23	90
Main pulmonary artery	23	97
Left pulmonary artery	24	96
Femoral artery	52	97

TABLE 4

VENTRICULAR SEPTAL DEFECT

Nutrition in 16 Cases



The percentile table shows that the majority of patients were severely malnourished.

TABLE 6
HAEMODYNAMICS OF VENTRICULAR SEPTAL DEFECT

Case No.	Age	Cardiac Output (l./min.)	Cardiac Index (l./M²)	Shunt L——R (l./min.)	L——R Shunt as % of C.O.	Pulmonary Arterial Mean (mm. Hg)	Femoral Arterial Mean (mm. Hg)	Pulmonary Arterial Mean as % Femoral Arterial Mean	Arterial Saturation (%)	Pulmonary Arterial Resistance	Peripheral Resistance	Right Ventricular Work	Right Ventricular Work Index	Left Ventricular Work	Left Ventricular Work Index	Total Work Index	Cardio-thoracic Ratio	Weight (%)
1	2/12	1·0	4·3	0·76	76	58	53	109	58	2,636	4,227	0·8	3·5	1·3	5·7	9·2	61	−3
2	7/12	2·4	8·1	0·83	34	77	71	108	85	2,522	2,326	2·5	8·3	2·4	8·0	16·3	66	−3
3	3/12	See Table 5																3
4	4/12	1·5	5·4	4·5	300	42	70	60	92	618	3,813	0·8	3·0	4·0	14·3	17·3	59	3
5	9/12	1·1	3·2	2·0	182	67	77	87	89	2,279	5,432	0·7	2·0	2·5	7·0	9·0	63	3
6	3/12	1·0	4·1	0·5	50	50	71	70	93	2,724	5,802	0·6	2·8	1·2	5·2	8·0	62	3
7	2/12	1·1	3·7	0·9	82	26	73	35	93	1,057	5,313	0·4	1·3	1·1	3·7	5·1	56	−3
8	6/12	1·7	5·6	3·6	211	54	79	68	93	737	3,751	1·1	3·7	4·2	14·2	17·9	69	−3
9	8/12	1·6	5·0	6·3	343	33	69	47	87	340	3,457	0·7	3·3	7·4	23·0	26·3	58	−3
10	9/12	1·4	4·4	4·2	300	57	66	86	95	795	3,684	1·1	3·4	4·6	14·4	17·8	58	−3
11	8/12	2·6	8·6	3·0	115	30	65	46	90	466	1,950	1·4	4·4	3·1	10·0	14·4	60	−3
12	4/12	1·5	6·3	1·9	126	50	73	68	95	1,163	4,051	1·0	4·3	3·3	14·4	18·7	60	−3
13	11/12	2·8	7·5	1·3	46	56	68	82	85	1,338	1,905	2·0	3·2	3·1	5·0	8·2	61	−3
14	12/12	4·0	7·7	1·7	42	55	59	93	92	715	1,192	2·6	5·0	3·9	7·9	12·9	62	25
15	12/12	1·7	3·8	4·4	258	26	60	41	90	346	5,511	0·5	1·0	5·0	11·0	12·0	53	−3
16	12/12	3·7	7·8	3·1	84	18	74	24	96	209	1,610	0·4	2·0	6·9	14·6	16·6	46	50

since no faith can be put in the failure to traverse the ductus. An associated defect of this type therefore cannot be readily excluded in this age group by catheterization alone.

B. The Haemodynamics. These are summarized in Table 6.

1. THE PRESSURES. Except in infants with congestive failure at the time of study, the levels in the great veins and right atrium were normal by comparison with adult standards.

Right ventricular hypertension was found in all but one case (16) of the series; this was carried forward into the pulmonary circuit essentially unchanged. No case was found to have the 'relative' pulmonary stenosis occasionally found in older persons with large left-to-right shunts. Its absence is probably related to the severe clinical condition and elevated total pulmonary resistance found in these infants.

Normal pressure levels for this age group have not been published, but sporadic observations in this unit in infants with compensated aortic stenosis suggest that adult standards hold good at least as early as 6 months of age. Case 16 would be normal by these criteria. Comparison of the pulmonary arterial mean pressures with the mean in the femoral artery showed that the former was 68% or more of the latter in 10 of the 16 cases. The implication of this is that these 10 children would be considered as poor surgical risks by the criteria of Lillehei *et al.* (1955). This pressure relationship if abnormal does not appear to be associated with the clinically assessed severity of these cases, *e.g.*, by nutrition, presence of dyspnoea or cardio-thoracic ratio. A normal relationship, as seen in Case 16, was in a child who had the highest growth percentile and a normal (46%) cardio-thoracic ratio. As expected, there is a suggestive relationship between a high mean pulmonary femoral pressure and the presence of arterial desaturation. However, as in Case 14, full saturation may be present even if the pulmonary arterial pressure mean is 93% of that in the femoral vessel.

Perusal of the peripheral saturation values, however, does show that significant oxygen unsaturation was present in seven of the 16 cases. This is again a contraindication to surgery in the views of Lillehei and his colleagues.

The pulmonary wedge pressures, where obtainable, were commonly within normal limits for the adult range.

2. CARDIAC OUTPUT AND SHUNTS. In the absence of control values for this age group, these figures are presented without comment. The high cardiac index in several of these children has been observed by us in older infants and children found to have no abnormality at cardiac catheterization. An index may be an unreliable concept in these small patients whose surface area is disproportionately greater per unit volume than in the adult. Additionally, the effect of the anaesthetic must be considered in the assessment of these results. The volume of shunt was three times or more the cardiac output in five of the patients and less than the cardiac output in six. As compared with older children studied in our laboratory, the left-to-right shunt is less in this group

which had a higher incidence of right ventricular hypertension. Conversely, right-to-left shunts were more common, and caused the high incidence of arterial unsaturation which has already been commented upon.

The resistances echo the phenomena already described; a high total pulmonary resistance was usual. This is in contradistinction to the normal or lower resistances found in many older children with a more benign lesion. Our only exception was Case 16, a patient who is perhaps more typical in this respect. The pulmonary arteriolar resistance (where calculable) contributes somewhat to this increase. The total peripheral resistances are in many cases high by adult standards, but this again may not be pathological for this group as it has been sporadically observed in normals of the same age studied in this department.

3. CARDIAC WORK. The right ventricular work was calculated on the assumption that the shunt occurs in systole and that this chamber does not contract upon the shunted blood. The results show that the amount of work done by the right ventricle is greatly increased by adult standards when expressed as a work index $\frac{\text{(R.V. work)}}{\text{(Surface area)}}$. This is, of course, a function of the raised pulmonary pressure. The left ventricular work is similarly increased by index values because of the left-to-right shunt.

Summation of the left and right ventricular work indices gives an estimate of the total work done by the heart in this condition. It is very likely, however, that values for normals in this age group are higher than for adults in this respect, because of the high peripheral resistance already mentioned, and the exaggerating tendency of a low surface area.

Discussion

This group illustrates the severe clinical and haemodynamic change in a series of infants with ventricular septal defect. It is seen that the problem in this age group is not of the shunt, but of the resultant or coincident pulmonary hypertension. This may occur very early in life. It was proven to exist as early as 2 months of age in Case 1. Clinically in this and in Case 3, the condition may have been present in the first two weeks of life. The resultant rise in ventricular and total work indices is very marked in the majority, and explains the high incidence of right-sided failure in this and other series (Engle, 1954). Growth failure is severe, but cannot be statistically related to the pulmonary arterial pressure if this is abnormal; nor in the absence of normal values to the cardiac output. If pulmonary pressure and arterial desaturation is considered in relation to operability, over half of these infants might not be aided by surgery. This trend might be reversed if these children are studied very early in life, though again cases occurred as early as 2 months in which surgery could not be advised. During the period of follow-up one child (Case 14) died of congestive cardiac failure; three others died suddenly at the beginning of a respiratory infection before surgery could be carried out.

Summary

The clinical and radiological features of a series of infants with ventricular septal defects are presented. The resultant effects on the haemodynamics are noted and discussed.

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SWEAT ANALYSIS IN FIBROCYSTIC DISEASE, CHRONIC PULMONARY DISEASE AND CONTROLS

BY

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Recent findings of abnormalities of sweat composition in patients with fibrocystic disease of the pancreas have stimulated broader interest in this disease and provided a new laboratory diagnostic procedure. A simplified method for collecting samples of sweat is presented, together with analytical results for sodium, chloride and urea concentrations in patients with fibrocystic disease and in patients with chronic pulmonary disease.

Previously described methods of sweat collection have required either special heating apparatus or controlled environmental humidity. Webb, Flute and Smith (1957) describe a method using enveloping polythene bags to encourage sweating and filter paper instead of pads of gauze to absorb the sweat.

The present method allows children to carry on with their normal activities during the collection. The small amounts of sweat obtained are adequate for analysis as the methods are the same as those used by Webb *et al.* with corresponding results. Gauze was found to be an advantage as the absorbed sweat and water did not require filtering before analysis.

The method described here, together with the analytical procedures, require no apparatus other than that available in any biochemical laboratory. In many centres the chloride content only of sweat is being estimated as this is considered diagnostic.

Patients Studied

Twenty children with proven fibrocystic disease of the pancreas, six children with chronic pulmonary disease unassociated with fibrocystic disease and six apparently healthy siblings of five of the fibrocystic patients were studied. Forty in-patients in whom there was no reason to suspect a sweat abnormality were selected as controls.

Method

The materials used were washed cotton gauze, transparent plastic sheeting and 1-in. wide waterproof adhesive strapping.

Ordinarily gauze contains small amounts of sodium chloride. All the 3-in. gauze squares used in the investigation were, therefore, prepared by first leaving them to soak in distilled water for two hours, and then completing the extraction of salt by passing approximately two gallons of distilled water through each 100 squares. They were dried at 70° C.

A dry 50-ml.-flask containing a gauze square and closed by a ground-glass stopper was weighed. This piece of gauze was placed over the lumbar region of the patient, the site having been washed with distilled water and dried. It was covered with a larger square of plastic sheeting the edges of which were fixed to the skin with adhesive strapping to make an airtight seal.

The gauze was left in position for two to six hours, depending on the temperature of the external environment. It was then returned to the flask and reweighed, the weight of sweat thus being determined. At least 0·1 g. of normal sweat is required for accurate analysis, although 0·06 g. is sufficient in cases of fibrocystic disease of the pancreas.

Five millilitres distilled water were added to the flask which was restoppered and left for 12 hours.

The solution obtained by compressing the soaked gauze with a glass rod and decanting was used for estimating the chloride by mercurimetric titration, the sodium by flame photometry and the urea by urease and nesslerization. With very small amounts of sweat, extraction was performed by centrifuging the gauze in a tube containing a 1 cm. length of narrow bore polythene

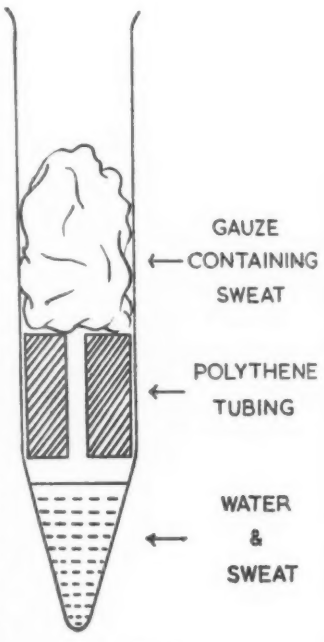

FIG. 1.

TABLE 1
MEAN VALUES AND RANGES OF SODIUM AND CHLORIDES

Group	Number of Cases	Range		Mean Values	
		Sodium (mEq/l.)	Chloride (mEq/l.)	Sodium (mEq/l.)	Chloride (mEq/l.)
Controls	40	6·6– 37·6	6·0– 38·4	21·2	21·8
Fibrocystic disease	20	36·4–189·4	49·6–196·1	104·0	111·5
Children with chronic pulmonary disease	6	48·1– 69·4	20·6– 40·5	58·2	31·5

tubing fixed in a conical centrifuge tube (Fig. 1). On centrifuging, the sweat and water passed through the polythene tubing into the small chamber below, from which it was removed with the aid of a Pasteur pipette.

Results

Sodium and Chloride Concentrations. Mean values and ranges are summarized in Table 1, and the correspondence between sodium and chloride concentrations in individual specimens is shown in Fig. 2. It is evident from the graph that the concentrations of sodium and chloride are much greater in the children with fibrocystic disease than in the controls.

Sweat from six children with chronic pulmonary disease showed high sodium but normal chloride levels. This may be an important finding but its significance is not apparent at the moment.

Six siblings of children with fibrocystic disease were investigated. All were healthy with no clinical evidence of disease. Two of these children were from one family, one having normal and one abnormal sweat. The remaining four were unrelated and of these three had abnormal, and one normal, sweat.

Urea Concentration. Sweat samples from 24 children were also analysed for urea, the results being summarized in Table 2.

There was a similar wide range of urea concentrations in both normal and fibrocystic groups, with an average concentration in the controls of 181 mg./

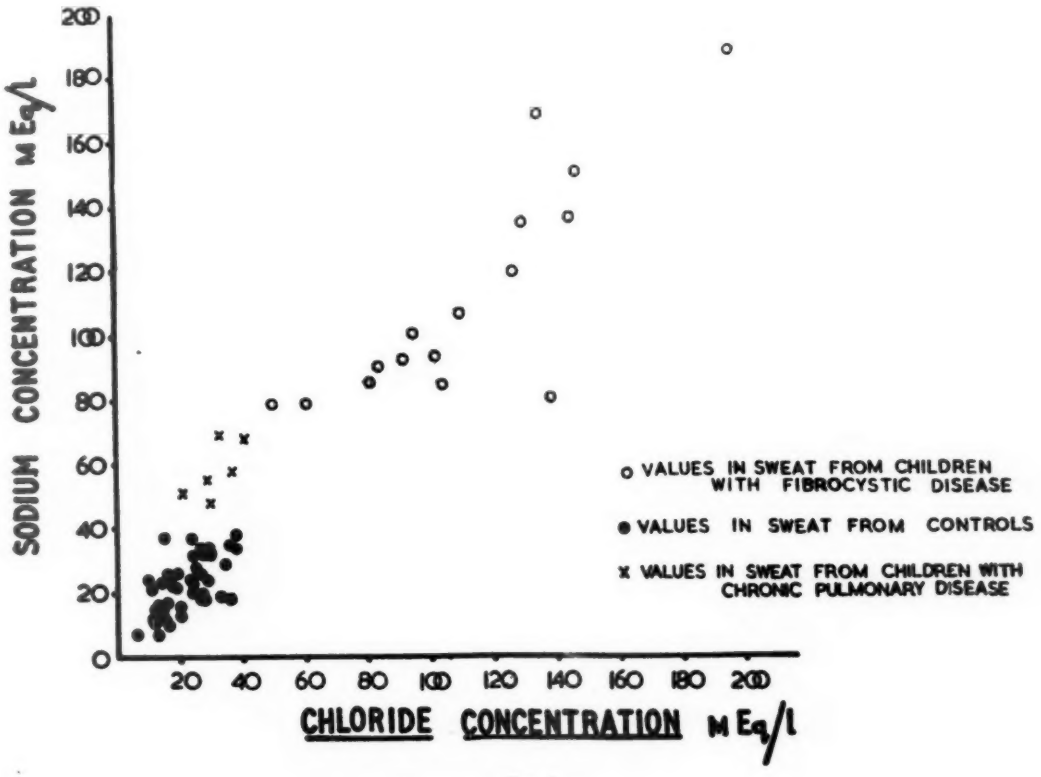

FIG. 2.

TABLE 2
RESULTS OF UREA ANALYSIS

Group	Number of Cases	Urea	
		Range (mg./l.)	Mean (mg./l.)
Controls ..	13	63–339	181
Fibrocystic disease	11	47–370	191

100 ml. and 191 mg./100 ml. in the group of fibrocystic children. Repeat estimations were performed on several children. The results were often far removed from those obtained originally, thus confirming that sweat urea concentrations vary in the individual though tending to exceed blood levels, *e.g.*, in one child with a raised blood urea (78 mg./100 ml.) the sweat urea was 755 mg./100 ml.

Amino-acid Concentration. The amino-acid pattern of the sweat estimated by paper chromatography was similar in both normal and fibrocystic groups and corresponded with the pattern shown by Dent and Walshe (1954).

Discussion

Since the occurrence in 1948 of heat prostration in 10 children of whom five had fibrocystic disease (Kessler and Andersen, 1951) many papers on abnormal sweat have been published.

The results of di Sant' Agnese, Darling, Perera and Shea (1953), who presented a series of 43 patients and 50 controls, and those of Schwachmann (1956), who investigated 200 patients and 800 controls, show that the concentrations of sweat sodium and chloride in fibrocystic disease are two to four times higher than normal. A similar difference has been obtained in the present series although the range of normality is lower than in previously published papers. This may be due to different methods and conditions of collection. Therefore it would appear that each investigator should establish his own standard according to his method.

The way in which the sweat becomes abnormal in patients with fibrocystic disease and in some of their relatives is unknown. Di Sant' Agnese *et al.* (1953) demonstrated by metabolic studies that disturbance in neither renal nor adrenal function was responsible, and no change could be seen in the sweat gland when examined microscopically.

Gochberg and Cooke (1956) came to the conclusion that the increased concentration of sodium chloride in sweat from fibrocystic children was due to an increase of sodium chloride in the precursor solution and suggested that there might be an absence of an enzyme, co-enzyme or substrate in secretory cells altering the release of energy producing the abnormal secretion. In this paper he reported sweat urea concentrations in nine children with fibrocystic disease, finding an average of 58 mg./100 ml. in controls and 55 mg./100 ml. in fibrocystics with little variation.

Examination of the sweat is becoming one of the most useful and reliable diagnostic tests for fibrocystic disease as illustrated by the two cases described.

Case Reports

Case 1. For three weeks before admission a girl aged 13 months had an exacerbation of the cough present since birth. There was no history of abnormal stools. She was cyanosed and febrile with crepitations heard over both lung fields. Radiographical changes were those of bronchopneumonia.

Analysis of the sweat on two separate occasions gave values typical of those in fibrocystic disease, viz.:

Sodium 92·5 mEq/l.	Chloride 170·0 mEq/l.
Sodium 142·0 mEq/l.	Chloride 86·2 mEq/l.

A three-day fat balance showed normal fat absorption, there was no excess fat in the faeces on microscopic examination, and the 'lipiodol' test (Silverman and Shirkey, 1955) was not indicative of fibrocystic disease.

Treatment was of no avail and the patient died three months after admission. At necropsy the findings in the pancreas and lungs were typical of fibrocystic disease.

This case resembles one reported by di Sant' Agnese (1955).

Case 2. A boy aged 9 weeks was admitted with suspected fibrocystic disease of the pancreas. He had passed pale, fatty and offensive motions and had failed to thrive. Radiological examination of the lungs revealed bilateral basal consolidation, fat globules were seen in the faeces on microscopical examination, and analysis of the fasting duodenal contents showed no trypsin and a very low activity of lipase.

Despite these findings repeated analyses of the sweat at monthly intervals gave normal results:

Sodium 12·9 mEq/l	Chloride 6·8 mEq/l.
Sodium 13·3 mEq/l.	Chloride 15·9 mEq/l.
Sodium 36·4 mEq/l.	Chloride 31·2 mEq/l.
Sodium 18·5 mEq/l.	Chloride 23·3 mEq/l.

His general condition improved slowly and his motions became normal without treatment. Subsequent analyses of the duodenal fluid revealed first low, and finally normal, activity of lipase and trypsin. It appeared, therefore, that the pancreatic dysfunction had been temporary.

Two other cases, brothers, attended this hospital during recent years. The elder boy had a splenectomy in 1953 when a diagnosis of portal hypertension with oesophageal varices was made. Subsequently he developed a severe pulmonary infection and in 1956 his sweat was found to contain high concentrations of sodium and chloride. His brother, who was thought to have coeliac disease in 1951, was readmitted in 1953 with faecal impaction which necessitated laparotomy. He has since been found to have fibrocystic disease of

the pancreas with abnormal sweat. A third child in the family died when 12 days old.

Summary

A simple method of sweat collection is outlined.

Two cases are described in which investigation of the sweat was helpful diagnostically.

The results fall into three groups: sweat from children with fibrocystic disease containing salt in concentrations two to four times that of the concentration in the control group, and children with chronic pulmonary disease having a normal chloride concentration in the sweat but a high sodium value.

There is no difference between the amino-acid and urea concentrations in controls and children with fibrocystic disease.

We would like to express our gratitude to Professor J. M. Smellie, Mr. H. B. Salt and Dr. O. H. Wolff for their encouragement and helpful criticism; to Mr A. E. Marston, Chief Pharmacist, for providing the salt-free gauze; to Mr. J. G. Williamson for the photographs; and to the consultant staff of the Children's Hospital, Birmingham, for permitting us to investigate their patients.

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THE GASTRO-OESOPHAGEAL REGION IN INFANTS

OBSERVATIONS ON THE ANATOMY, WITH SPECIAL REFERENCE TO THE CLOSING MECHANISM AND PARTIAL THORACIC STOMACH

BY

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(RECEIVED FOR PUBLICATION MAY 24, 1957)

The nature of the closing mechanism between the oesophagus and the stomach has attracted considerable anatomical study in the past 300 years. Main interest has centred on the adult; the anatomy of the infant, which does not necessarily correspond, has not received the same attention. The present investigation is therefore concerned with infants. It was undertaken with two objects: first, from the anatomical study, both macroscopic and microscopic, to assess the importance of the various components of the normal closing mechanism; secondly, to consider the abnormal infant, in whom this mechanism is incompetent, in the light of clinical experience and radiological observation.

Material

The diaphragm, lower oesophagus, upper stomach, aorta and surrounding tissue were removed *en bloc* from 115 human subjects and fixed in 10% formol saline. Every specimen was carefully dissected and drawings were made of the essential features in all. Histological confirmation was obtained in doubtful cases. In age, the patients varied from a 32-week foetus to 8 years. In the great majority the ages ranged from a few hours to 1 month (average weight of 5½ lb.). One foetus of 1 lb. 2 oz. and one girl of 13 years were also studied. The sexes were about equally represented. In addition to the dissected specimens, numerous studies were carried out in the necropsy room where the organs were examined *in situ*. The following observations were made.

Diaphragm

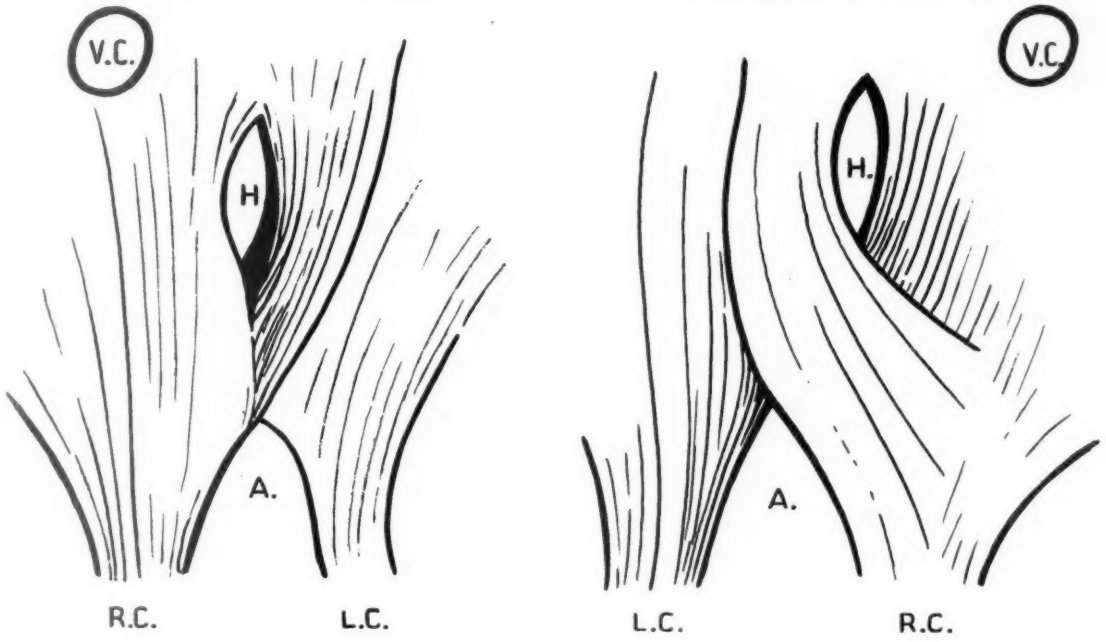
Anatomy textbooks describe, and interesting pictures convincingly show, decussation of the crural fibres dorsal to the oesophagus. This is rare. Only a few specimens were found where the overlap of muscle fibres at their origin from the median arcuate ligament in the standard type could possibly be mistaken for decussation. Low (1907) and Collis, Kelly and Wiley (1954) found no decussation in a series of 25 and 50 diaphragms respectively. Considerable normal variation occurs, the functional significance of which has not been fully appreciated.

The Standard Pattern. The aorta, a midline structure, divides the crura into a right and left crus (Fig. 1a, 1b, 4). The right crus is better developed, more fleshy and wider than the left one. It arises from the bodies and discs of the upper three or four lumbar vertebrae (sometimes five); it passes cranially and divides into a large right and a smaller left limb which embrace the gullet and join again anteriorly. The fibres of the right limb arise from the vertebral column and right border of the median arcuate ligament and run straight upwards to insert into the central tendon. The right limb is always anterior. The spinal fibres of the left limb run upwards behind the right limb, arch obliquely over the aorta and then ascend immediately to the left of the gullet to insert into the central tendon. The lateral fibres of the left limb are short and arise from the central portion of the median arcuate ligament. The medial fibres sometimes curve acutely to the right, caudal to the oesophagus to gain origin from aponeurotic fibres to the right of the hiatus. The right limb is therefore visualized from the ventral aspect whereas the left limb can only be displayed fully from the back (Fig. 1b, 4). This arrangement results in a perfect overlap. The twisted figure of eight which is so well depicted in most drawings was not seen in a single instance; one must therefore conclude that it is not an anatomical fact. On the contrary, the 'straight' arrangement of the fibres is usually conspicuous.

The left crus is small and almost separate from the lateral fibres of the left limb; it takes no part in the formation of the hiatus. Decussation of muscle

(a) The standard pattern seen from the abdomen.

(b) The standard pattern seen from the chest.



(e) Stage 1 shift to the left.

(f) The broad dorsal band consists of almost half the fibres of the left crus.

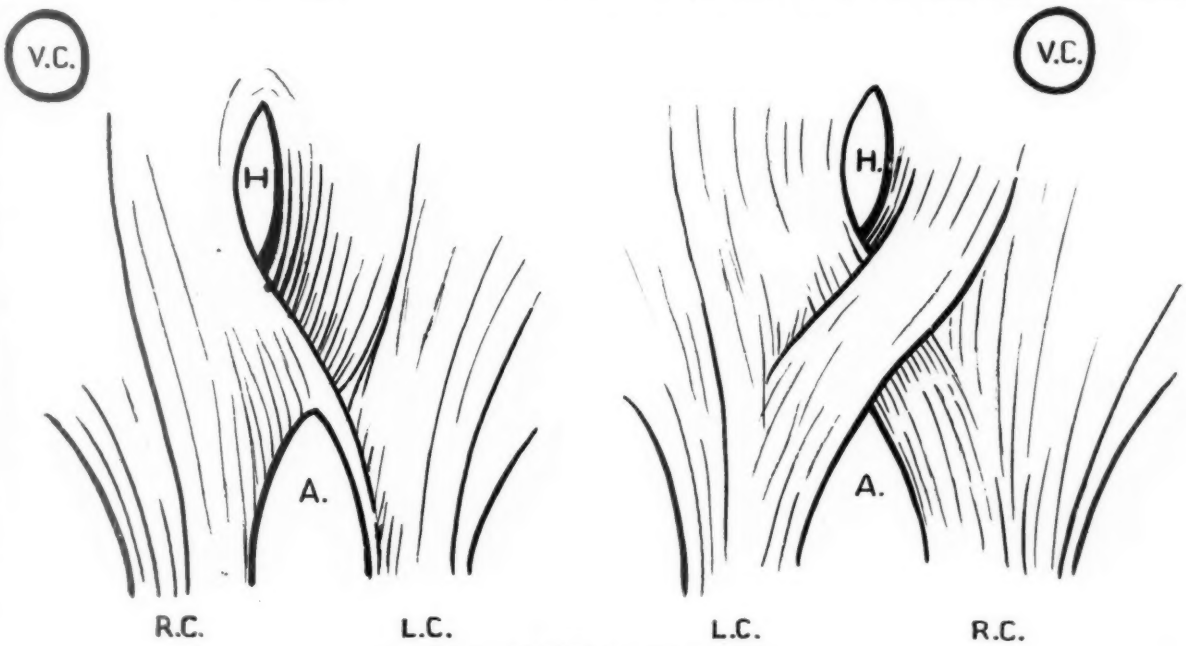
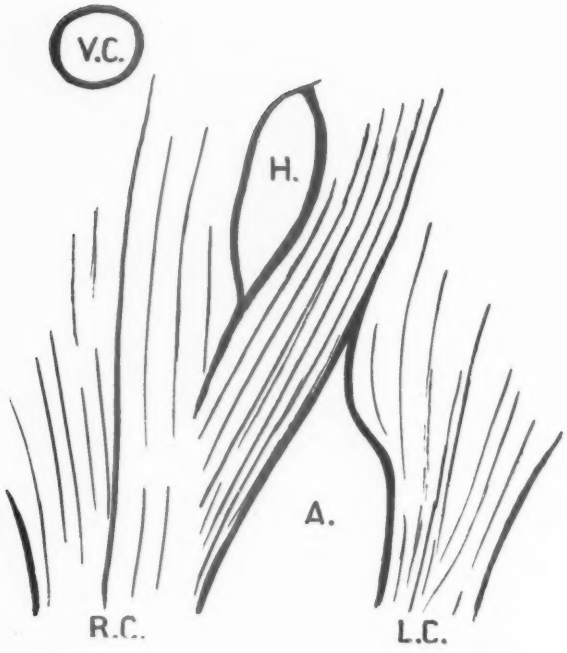


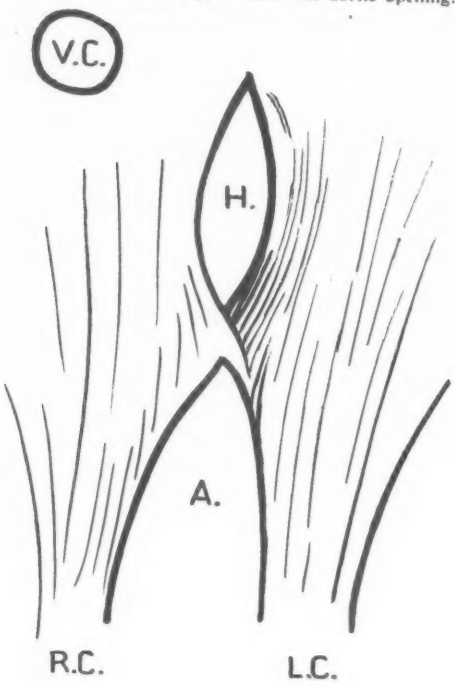
FIG. 1.—Variations in crural anatomy

R.C.=right crus L.C.=left crus A.=aortic opening H.=hiatus V.C.=vena cava

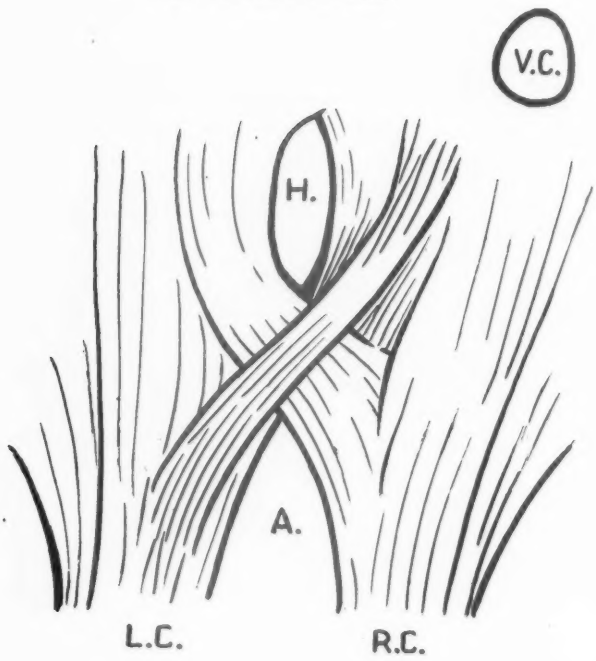
(c) Shift to the right.



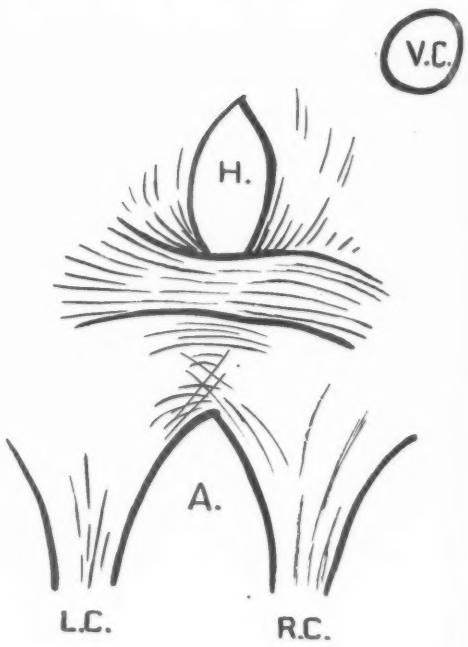
(d) A large hiatus approximates the aortic opening.



(g) A narrow dorsal band.



(h) A transverse band.



fibres does not occur dorsal to the hiatus, but is often present where the fibres arise from the median arcuate ligament.

Deviations from the standard pattern are very common.

Shift to the Right. In this variation, instead of the ventral and dorsal 'waistcoat effect' of the standard pattern, the right crus merely splits into two limbs so that a pyriform hiatal opening is formed (Fig. 1c). There is little or no overlap. The left limb does not arise from the median arcuate ligament, which is non-existent, but itself forms the right border of the aortic opening. The left crus is small and takes no part in the hiatus.

Shift to the Left: Stage 1. The medial fibres of the right crus sometimes transgress the midline to gain origin from the left border of the arcuate ligament (Fig. 1e). This encroachment on the left side may be slight or so complete as to extend down to the tendinous origin of the left crus, but essentially it remains part of the right crus. The left crus still does not partake in the formation of the hiatus.

The Scissors Overlap: Stage 2. The right and left crura may be equally well developed, but commonly the right one is still bigger. The left crus, which is for the first time taking part in the formation of the hiatus, forms a perfect overlap by criss-crossing with the right crus. The most common variation is a broad band from the left crus which crosses anteriorly to form the right hiatal margin, supplemented by a posterior band from the right crus which forms the left hiatal margin. These bands constitute the 'scissors'. They are easily separated and run antero-medially on each side of the aorta as the right and left borders of the median arcuate ligament which, as such, is non-existent. The treble or quadruple overlap when three or more bands criss-cross, is more uncommon (Fig. 2). The relative size and origin of the bands vary tremendously and no two are quite alike.

FIG. 2.—A triple 'scissors' overlap.

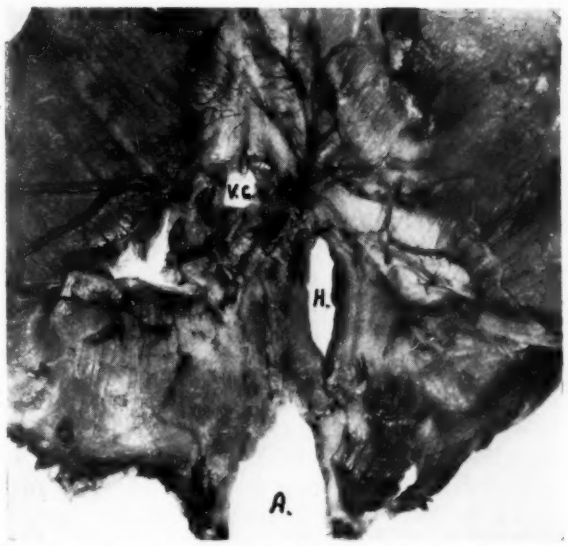


FIG. 3.—Stage 3 to the left. Diaphragm seen from the abdomen.

The Hiatus Formed Completely by Left Crus: Stage 3. This variation must be relatively uncommon. It was encountered in only one specimen and no previous descriptions of it have been seen. The left crus formed the entire hiatus and presented a mirror image of the 'shift to the right' (Fig. 3). There was no overlap in this case.

Accessory Bands. Low (1907) first described an accessory muscle band, 4 mm. wide, that extends from the superior aspect of the left crus, in front of the aorta and within the fibres of the right crus, to the caval orifice. He found four of these bands in 25 specimens. In an excellent paper Collis and his colleagues (1954) described a variant of Low's band as well as a transverse inter-tendinous bundle which they displayed in dissections of 50 diaphragms. Examples of all three types were found in this study, as well as other variants (Figs. 1f, 1g, 1h). The Low bands varied from a few muscle strands to a

TABLE 1
NORMAL VARIATIONS IN THE PATTERN OF THE CRURA

Crural Pattern	Standard Type	Shift to the Right	Shift to the Left: Stage 1	Shift to the Left: Stage 2	Shift to the Left: Stage 3	Accessory Bands	
						Small	Large
Total 115	67	12	28	7	1	20	19
Percentage ..	58·6	10·3	24·2	6	0·9	34	

bundle as thick as the left limb of the right crus and then formed a powerful 'scissors overlap'. The fibres either passed to the right, superficial to the right crus (the great majority), or through the substance of the left limb or lay in front of it. The obliquity varied from almost vertical to almost transverse. Some bands were long, thin and insignificant; other bundles were short, flat and powerful. Whereas most of the small bands are of academic interest only, there can be little doubt that on contraction they tend to decrease the size of the hiatal opening. When well developed, they may become an important factor in, first, enhancing the supportive function of the crura to maintain gastro-oesophageal competence and secondly, to reinforce the posterior weak spot in the hiatus.

The postero-medial branches of the phrenic nerves are the sole motor supply to the crura of the diaphragm (Botha, 1957a). Each nerve innervates the muscle on the ipsilateral side of the hiatus irrespective of its origin.

Table 1 indicates the wide variation that exists in crural pattern.

The Median Arcuate Ligament. In the standard type it is tendinous, well developed and gives origin to crural fibres from both sides. It does not always form the arching 'ligament' so well figured in text-books. It is weakest in the 'scissors' type (Fig. 2) or when the hiatus has shifted to the right and may sometimes be completely absent. In a few dissections the tendinous crural fibres joined in the midline, posterior to the aorta, and thus formed a fibrous ring for the passage of this big vessel.

Overlap. This is one of the most characteristic features of crural architecture and is by far most marked in the standard type. It obviously serves three purposes:

(1) TO STRENGTHEN A POTENTIALLY WEAK AREA. Anteriorly the crura are inserted into the central tendon by short, decussating, musculo-tendinous fibres. Clinical weakness never occurs at this site and therefore no anatomical overlap is indicated. Posteriorly, however, there is little stability and the criss-cross fibres might be easily separated by a force that acts on the hiatus. This is only too well demonstrated by the frequent occurrence of hiatus hernia in late adult life. Overlap is still Nature's best way of providing the greatest protection for the weakest area with the minimum available tissue.

(2) RIGHT LIMB ALWAYS OVERLAPS ANTERIORLY. This creates an oblique hiatus which is essential to accommodate the lower oesophagus with its marked deviation to the left. Overlap is not the cause of the obliquity of the gullet, as this is present if there is poor or no overlap (as found in some types), but it maintains its position more firmly and embraces the oesophagus more snugly during diaphragmatic or swallowing movements. A secure fixation decreases the chances of herniation.

(3) OVERLAP CHANGES ALIGNMENT OF MUSCLE FIBRES. This is specially noticeable in the 'scissors' type where not only the longitudinal, but also the transverse diameter of the hiatus is decreased when the diaphragm contracts. In the standard type, the right limb mainly pulls caudally, but the left limb pulls down and to the right, thus narrowing the hiatus from side to side. This tendency to constrict the hiatus is least marked in stage 3 and 'shift to the right', which on theoretical grounds should therefore be inferior functionally.

The Hiatus. Unlike the adult, the hiatus in the infant is of very uniform size. In all the above dissections, it was small, so small that the narrowest portion of the oesophagus could just pass through (Fig. 4). The oesophagus was gripped firmly.

The presence of a hiatal tunnel in the adult is doubtful. In the infant it is a fact. The crural muscle is round and 'heaped up' at the hiatal margins especially on the right side. In the 7 cm. embryo the length of the right hiatal wall is twice the diameter of the oesophageal opening (Botha, 1958). This length gradually decreases as the foetus develops, but it is still well marked at birth. The length of the canal depends on the degree of obliquity. Where no overlap is present, the hiatus consists of a straight hole through the diaphragm (Fig. 3). The obliquity can easily be seen when the diaphragm is looked at from the front. The hiatus appears as a small, ovoid slit, which sometimes almost disappears (Fig. 4). When viewed obliquely

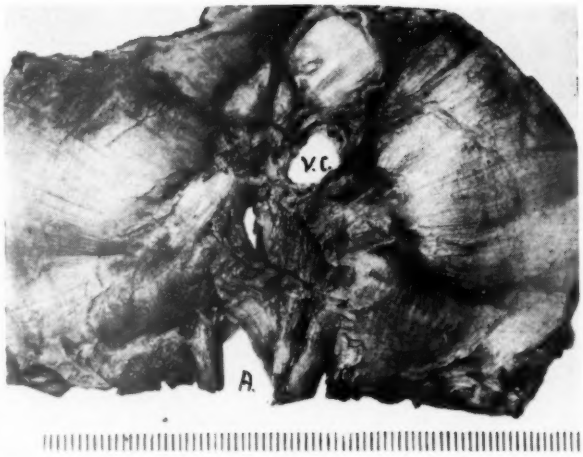


FIG. 4.—The hiatus in the standard pattern is slit-like when seen directly from above.

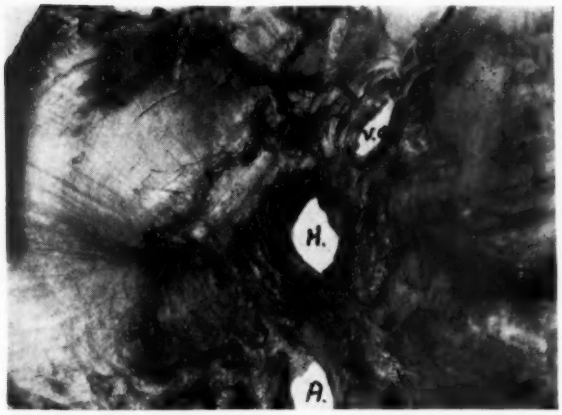


FIG. 5.—The hiatus in Fig. 4 appears large and ovoid or round when viewed obliquely.

in the line of the tunnel, the true size becomes apparent (Fig. 5). As in the adult, but less marked, the anterior wall of the canal is much shorter than the posterior one. This is primarily due to the wide overlap behind and the oblique upward slope of the diaphragm. In the older subjects in this series the canal was relatively shorter, wider and the oesophagus less securely fixed. In infants it was mostly from 3 to 8 mm. long, and proportionately much longer and firmer than in the adult.

The relative distance from the aorta to the caudal margin of the hiatus is also much greater in the infant than in the adult, suggesting that with age the oesophagus gradually approximates to the aorta. This is most certainly due to opening of the overlap and attenuation of the muscle fibres. In one specimen the median arcuate ligament and the inferior hiatal margin were very close together (which is most unusual in infants) and no overlap was present. In addition, the hiatus was relatively big (Fig. 1d). Although the oesophagus was firmly attached in the crural tunnel, this type of diaphragm with short fibres, lack of overlap and a wide hiatus may in future, when the necessary strain is present, give way to herniation.

Phreno-oesophageal Membrane. Any doubt as to the existence of this structure would be quickly dispelled by an examination of the infant diaphragm. There is no basic difference in its formation, position and attachments from that in the adult. It is, however, a much more definite structure that could be seen in every specimen as a thick, closely woven, creamy-white layer that bridged the potential gap between diaphragm and oesophagus. The main component is formed by the well-developed subdiaphragmatic fascia that divides at the level of the hiatus into a short, stout inferior limb and a thinner, long superior limb. The lower portion is usually stronger and is easily seen after removal of the fat and peritoneum as it splays out to a broad insertion into the cardia and adjacent stomach. The superior limb passes upwards through the hiatus and is joined above by the supra-diaphragmatic fascia which is a very definite layer but less well developed than its counterpart below. This strengthened limb then ascends in a circular fashion to insert into the terminal 5-10 mm. of thoracic oesophagus. The insertion of the membrane is never abrupt but in successive concentric layers of elastic strands with small areolar spaces in between. Individual strands are tough and can withstand considerable pressure. Some appear to be attached to the outer connective adventitia of the oesophagus, fascia propria, whereas others penetrate the external lomgitudinal muscle coat and can be traced down to the submucosa. The greatest concentration of fibres is inserted immediately above the diaphragm. Fat is absent in this structure.

The importance of this structure, which has been called a figment of the imagination, cannot be overestimated. It is the sole fixation of the oesophagus in the diaphragmatic hiatus, as the supportive value of the serosal layers above and below is negligible. The stomach and oesophagus were soundly secured in every specimen that I dissected, yet sufficient resiliency was present to allow adequate physiological movement. Fixation was much more firm in infants and movement was less than in children, and even more noticeable when compared with the adult. This difference is essentially due to the anchoring ability of an unattenuated phreno-oesophageal membrane and secondly, to a narrow, tight-fitting hiatus.

This structure is not a ligament. It is a fibro-elastic layer which is specially adapted to stand the strain of incessant movement at the hiatus during diaphragmatic contraction for 70 or 80 years. The histological appearance of the elastic fibres as well as their ratio to collagen is the same as that of a normal adult. Commonly 40-60% of elastic fibres occur but the proportion varies from 10 to 90%. The fibres vary in size, shape and form. Short, stout, blunt-ended strands appear next to thin, long filamentous fibrils. They vary from place to place and are mostly single. Branching does occur but is not marked. Resiliency and strength are obtained by wavy intertwining of the strands. As the fibres run in lamellae or bundles, different layers may be recognized on cross section.

Lower Oesophagus

Anatomically the lower oesophagus can be divided into a supra-diaphragmatic portion, a narrowed hiatal area and the abdominal oesophagus (Fig. 6).

The Supra-diaphragmatic Portion. This part of the oesophagus was generally wide and in the majority the diameter gradually decreased towards the diaphragm. In the older children it appeared wide right up to the hiatus. In only one specimen (a stillborn female of 9 lb.) was there a definite saccular dilatation above the diaphragm. As in the adult, the 'phrenic ampulla' is not an anatomical entity. It must be regarded as a radiological concept for a physiological phenomenon.

The Area of Constriction. In almost all the specimens a constricted area on the oesophagus coincided with the diaphragmatic hiatus which is always terminal in infants. The crura fit tightly around the oesophagus immediately above the cardia so that the abdominal part of this organ is very short. As the infant grows, the abdominal oesophagus increases in length so that the area of constriction shifts proximally. A narrowing was also observed in specimens where the oesophagus was removed from the diaphragm before fixation in formalin, but it was never so pronounced as when the specimen was fixed with the organs *in situ*. This clearly suggests that the diaphragm is mainly responsible for the localized area of constriction, but that another factor is present as well. This factor is the inferior oesophageal sphincter. Evidence of an anatomical sphincter was found in a small proportion of these subjects (Fig. 7). The fibres are thick, coarse and more irregular. Interlacing and cross bundles are common. The width depended on the age, but it was mostly 5 mm. wide

FIG. 6.—The lower oesophagus: the arrows indicate the crural tunnel.

in infants, and could only be inspected properly if the mucosa was removed. It was more difficult to see this in small specimens, but in the older age groups it became more evident. Sometimes it began at the oblique fibres, but in most cases it was above and separate from this bundle. In one specimen, a definite ring-like muscle band of 3 mm. wide was found a few millimetres above the cardia.

The Abdominal Oesophagus. In the 18 mm. embryo the abdominal oesophagus is half as wide as the stomach and almost as long as the lesser curve of this organ (Botha, 1958a). When the embryo is 9·5 cm. long, it is still very well marked. Gradually the abdominal oesophagus gets shorter. At birth it is so short as to be almost non-existent in some cases. After a few months it is usually a few millimetres long and within a few years it measures from 5 to 15 mm.

The left wall is short or non-existent. The right wall is long and curves towards the left in a characteristic fashion to join the lesser curve at the cardia. The distal widening before the oesophagus joins the stomach is slight in the infant, but becomes more apparent in the first five to 10 years.

FIG. 7.—The inferior oesophageal sphincter after removal of the mucous membrane.

Cardia

The site where the oesophagus joins the stomach is called the cardia, and in infants it is always well defined. It is narrow in the infant but wider in older children. Internally, the sling fibres are the only guide as to the level of the cardia. They were present in every specimen, but better developed in some. These fibres are already macroscopically evident in the 8 cm. foetus, and form a much sharper ridge in the infant than in the adult.

Cardiac Angle

Several angles are formed by the foregut in the region of the diaphragm. The most widely discussed of these is the gastro-oesophageal angle (cardiac angle or incisura of His, 1903) which is formed on the left side between the abdominal oesophagus and the gastric fundus. Unfortunately this is often confused with the lower oesophageal angle which is formed at the hiatus as the abdominal oesophagus deviates to the left. The other angle is formed by the almost vertical oesophagus entering the stomach which lies at an oblique, horizontal plane.

The first angle is very variable. Its acuteness mainly depends on the fullness of the stomach. In the empty organ it is mostly more than 90°. In the full stomach, especially when a large gastric air bubble is present, the fundus rises higher and bulges medially so that this angle becomes more acute; but even in a full stomach it may still be a blunt angle.

Serosa

The peritoneal reflections in the infant are similar to those in the adult.

Fat Pads. Subperitoneal fatty deposits around the cardia are commonly present in the adult and especially large and lobular in obese individuals with a lax hiatus. These fat pads are either very small or absent in children and infants.

Gastro-phrenic Band. This was present, at least to some extent, in all the specimens. It is formed by a double fold of peritoneum that extends to the left from the abdominal oesophagus and fixes the superior border of the fundus to the under surface of the diaphragm. Sometimes this fold is narrow and almost non-existent. Commonly it forms an appreciable layer and may even extend as far laterally as the spleen. Loose, areolar connective tissue and elastic fibres are present, especially near the hiatus. Histologically the structure resembles

closely the phreno-oesophageal membrane, except that elastic fibres are not nearly so abundant.

Infracardiac Bursa. Persistence above the diaphragm of the pneumato-enteric recess on the right side is common (Fig. 8). In this series 16 mesothelial-lined cavities were found of which seven were quite big. Histological sections proved the serosal lining. In two of these the cavity extended downwards on the right of the oesophagus, through the hiatus into the lesser omentum, where it ended blindly. In none of the present series was any freely communicative sac with the peritoneal cavity found, but this was demonstrated in adult dissections. These serosal pockets or bursae are uncommon in adults, which indicates that most are obliterated after birth.

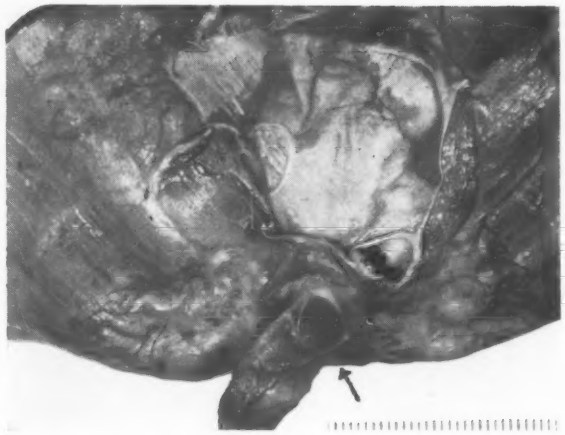


FIG. 8.—Infracardiac bursa on the right of the oesophagus seen from above.

Mucosa

Great variation occurred in the level at which the squamous epithelium changed to gastric mucous membrane. In the great majority the change took place near the gastro-oesophageal junction. In 63% the change took place at the cardia. Although the squamous epithelium was never found to extend well down into the stomach (as in the horse, rat or pig), it did in some cases descend below the cardia for a few millimetres. In 33% the change was above the cardia and in 4% it was well above the cardia. In 69% it occurred below the diaphragm, in 27% at and in 5% above.

The junction was usually clearly visible as a serrated, irregular line where the smooth, pale, stratified squamous epithelium changed to the darker, more granular, glandular mucosa. In some cases, however, it was almost impossible to define the junction on macroscopic examination. The junction lies obliquely in the line of the cardia and is therefore always more distal on the right side.

Longitudinal oesophageal folds are tightly pressed together and no change occurs up to the cardia. There the folds terminate in small irregular triangular pads that radiate away from the cardiac orifice. The gastric folds begin separately at this level, and sometimes appear puckered and bunched up at the level of the hiatus. The folds bear no relation to the level of mucosal change. Even in those cases where this level does appear above the cardia, no alteration can be seen in the longitudinal arrangement of the oesophageal folds. It is quite certain that the site of mucosal change (as distinct from the cardia) cannot be located by *x*-ray examination.

Discussion

The Closing Mechanism. The exact role of the diaphragm, as a factor in preventing abnormal reflux of gastric contents in the adult, is still a matter of dispute. From the present dissections, however, there is little personal doubt as to the important function of the diaphragm in assisting the gastro-oesophageal closing mechanism of the infant. The crural muscle fibres are long, thick and well developed. The excellent overlap provides a small hiatus which is very oblique and relatively long. This, together with a tough, unstrained phreno-oeosophageal membrane ensures firm fixation. The short, almost non-existent abdominal oesophagus minimizes movement and rests snugly in the crural canal. The diaphragm thus forms a most important accessory mechanism which acts during all phases of respiration, although the marked overlap and criss-cross of the broad, stout bundles must result in a maximum constriction when it contracts. Compared with the adult, this special adaptation appears very necessary at the beginning of life. The infant is almost always supine. The stomach is relatively small, and filled every three or four hours with fluid and excess gas. Furthermore, the closing mechanism is frequently subjected to sudden bouts of raised intra-abdominal pressure during crying, hiccoughing or defaecation. Despite this, competence is excellent. In fact, competence is so remarkable that even the conventional posture and traditional tap on the back might sometimes fail to dislodge the gas bubble for five or 10 minutes after a feed. When the gas bubble eventually escapes, it does so with a characteristic burst which is easily perceptible by the flat of the hand on the abdomen; and deflation is as rapid as pricking a balloon. Practically speaking, cardiac incompetence in the normal infant is very uncommon. Thomsen (1955) examined 145 children (7 months to 7 years) radiologically, who were

admitted to hospital for diseases other than gastro-intestinal. Despite steep Trendelenburg and manual compression of the abdomen, reflux was never demonstrated. However, cardiac incompetence in infants with partial thoracic stomach (where support of the diaphragm is lost) is much worse than in adults with hiatus hernia. The excellent competence in infancy is therefore not primarily due to a superior closing mechanism, but to the more efficient function of a less attenuated hiatus.

The existence of a physiological inferior oesophageal sphincter is now well accepted (Lyons, Ellis and Olsen, 1956). In a combined cine-radiographic and manometric study of the gastro-oesophageal junction, Botha, Astley and Carré (1957) proved that this sphincter extends over a considerable segment of the lower oesophagus: it is not confined to the cardia alone. The present study supports these views. In a few specimens, definite macroscopical thickening was present in the circular muscle coat, but this was never confined only to the cardia. These anatomical sphincters should not be compared with the pyloric sphincter as a standard. It is furthermore essential to remove the mucous membrane carefully before inspection of the muscle. Lerche (1950), who conducted a similar investigation in adults, concluded that anatomical sphincters do exist. Histology is notoriously unhelpful in the localization of anatomical sphincters and their presence cannot be refuted on microscopy alone.

The cardiac mucosal folds in the infant appeared without exception to be of a rosette pattern. Minor variations were frequent but no special folds, as seen in the adult, occurred. There were no 'curtains' on the greater curve side and no evidence to suggest a valve mechanism. The cardiac orifice was mostly round: the centre of symmetrically radiating mucosal folds. These folds are bunched together by the inferior sphincter so that a watertight seal is formed at the cardia. Together, these two factors act in perfect harmony and constitute the normal closing mechanism between stomach and oesophagus (Botha, 1958b).

Partial Thoracic Stomach

It has been shown that cardiac competence and oesophageal fixation are proportionately much better in infancy than in the adult. A partial thoracic stomach which causes vomiting immediately after birth is therefore not merely a 'slight herniation', but a major derangement.

The occurrence of part of the stomach in the posterior mediastinum was before considered to be rare in children. Thomsen (1949), who reviewed 70 reported cases up to 1947, published 58 cases of his own in 1955. Carré, Astley and Smellie (1952) found reference to just over 100 cases, yet they found an annual incidence of 18 infants with a partial thoracic stomach at the Children's Hospital in Birmingham. As there is no reason to suspect any recent alteration in the incidence of the condition, it is reasonable to assume that most cases have remained undiagnosed in the past. There are several reasons for this; sliding hiatal hernia has only become a recognized clinical entity over the last 20 or 30 years, and then mainly in adults. Many centres have lacked diagnostic facilities as well as experienced radiologists in this field. Recent advances in thoracic surgery have made this region readily accessible, when once the disorder is diagnosed. Another important reason for improved understanding of this condition is that a widespread interest in the oesophagus and closing mechanism has developed in the last decade, referred to in the American literature as 'esophagology'.

A considerable difference of opinion exists as to the aetiology of this abnormality. The mechanism of sliding hiatal hernia in adults has been admirably described by Allison and other workers in numerous publications. Partial thoracic stomach in infants has subsequently been regarded, without reservation, as a similar condition that developed in the same way. Husfeldt, Thomsen and Wamberg pointed out in 1951 that this explanation does not directly apply to children. The findings now recorded strongly support their view. The present confusion is considerable, partly because the evolution of the disorder is not fully appreciated. It is essential, therefore, first to point out why the mechanism of partial thoracic stomach in infants and that of sliding hiatal hernia in adults is not the same.

Evolution of Sliding Hiatal Hernia. The outstanding feature of the above anatomical observation, is the small, powerful hiatus with secure oesophageal fixation in marked contrast to the findings in the elderly. It is therefore not justified to discuss 'hiatal hernia' in infancy by referring to adult anatomy (Thomsen, 1955). It cannot be accepted that a normally developed and situated stomach with normal attachments would herniate through a normal hiatus, either shortly before or after birth, as a result of extrinsic forces that might act on the viscus.

Within the first few years of life, however, certain changes become manifest in the anatomical relationships of the cardiac region. The hiatus enlarges and the tunnel becomes shorter and less oblique. The abdominal oesophagus lengthens and becomes less securely fixed so that freer movement takes place.

These changes are even more exaggerated in the adult, due to the continuous strain on one of the potentially weak spots of the abdominal wall. The crural muscle becomes thin, stretched and weak. The force acting on the hiatus continually tends to enlarge the opening, separate the crural limbs and diminish the posterior overlap. The hiatal tunnel looses its obliquity, becomes shorter and wider until ultimately it constitutes a direct hole through the diaphragm. The phreno-oesophageal membrane stretches to a thin, attenuated layer, located only with difficulty. The elastic fibres are fragmented, dissociated and less wavy. This encourages greater mobility, so that on straining the cardia is forced into the hiatus and the aperture is further stretched, thus setting up a vicious circle. Small additional strains in the form of obesity, posture, constipation, bronchitis, corsets, etc., are sufficient to force the cardia progressively through the weakened hiatus until it lies in the posterior mediastinum. A benign situation then rapidly becomes significant. Displaced into an abnormal position, deprived of the important support of the diaphragm, the closing mechanism acts at a functional disadvantage; and when subjected to a sudden, forceful jet of gastric contents, it must give way in one direction only—into the oesophagus. As the sphincter weakens, reflux occurs more readily, until the sensitive squamous epithelium is continuously exposed to the relentless activity of gastric juice.

Oesophagitis follows. The acute inflammatory reaction is gradually followed by chronic fibrosis. The hernia increases in size, partly due to pressure from below and partly due to pull from above (the negative pressure, suction force and the remarkable longitudinal retraction of the outer muscle coat). As the cardia ascends the oesophagus maintains its straight contour, but gradually the lower portion is fixed in this position by ulceration and scarring; thus the patient ultimately ends up with a short oesophagus complicated by a stricture. The many variations on this theme need no elaboration.

In the vast majority of adults, sliding hiatal hernia is an acquired condition that usually develops in the later decades of life without any obvious congenital abnormality. It signifies a degenerative change in a normal hiatal region which is closely analogous to certain types of herniation of the anterior abdominal wall or pelvic floor and subject to the same predisposing causes.

Partial thoracic stomach in infants, I believe, is a congenital abnormality in the great majority of cases. The following facts substantiate this view.

Age Incidence. In the vast majority of infants with partial thoracic stomach (proved radiologically), symptoms date from birth or the early neonatal period: this in itself is highly suggestive of a congenital origin. In a series of 58 children with 'hiatus hernia', Thomsen (1955) found only three cases which presented after the age of 7 years. Two of these had para-oesophageal herniae (14 and 15 years) and therefore fall into a separate group and in the other child symptoms were present from birth. More than half of the infants in this series were admitted to hospital within the first year of life.

On the other hand, the incidence of sliding hiatal hernia in the 10-20 year age group without any previous symptoms is extremely small. If partial thoracic stomach is the result of simple herniation as in the adult, the incidence must increase, or at least some cases must present during this time, as the hiatus gets weaker with advancing age; the condition should not become rare.

Sex Incidence. Although Astley (1956) gives the sex incidence as equal, Thomsen (1955), Greenwald and Steiner (1929) and Truesdale (1935) found a much higher incidence amongst boys. In adult herniae, females predominate.

Familial Incidence. 'Enough familial instances occur to indicate a hereditary factor; in 10% there are one or more other cases in the family' (Astley, 1956). There may be as many as three infants in one family. The condition also occurs in twins (Wamberg, 1947) and in mother and daughter (Myles, 1939). No familial tendency has been noted in adults with herniation.

Radiology. The hiatus is sometimes unexpectedly small in adult sliding herniae. Where the hiatus is wide, a large portion of the stomach usually lies in the chest. As small herniae get bigger, reflux occurs more easily and stricture may develop.

The hiatus in infants with partial thoracic stomach is on the whole surprisingly wide; it is out of proportion to that in the adult. This lax, wide, and at times conical or tented hiatus contrasts very sharply with the normal crural pattern. With this wide gap, it is reasonable to expect further deterioration and increase in the size of the hernia as the infant gets older, if in fact, thoracic stomach is due to simple herniation. Instead, the supradiaphragmatic loculus remains small and insignificant in the majority of cases; it may even get smaller—or disappear completely. Regurgitation, however, is very free and competence relatively poor; the mechanism at the cardia is disturbed out of proportion to its radiological appearance. The fact that this wide hiatus later assists cardiac control with

greater efficiency suggests that a congenitally deranged or maldeveloped diaphragm might with advancing age become more normal either by further development or by accommodation.

Clinical Course. In adults symptoms often have no relation to the radiological appearance of hiatus hernia; the tendency, however, is to deteriorate. Just the opposite happens in infants. The great majority follow a benign course and become completely asymptomatic by the age of 5 years with no subsequent relapse in childhood. The incidence of stricture varies in different centres. Untreated it is less than 10%; with adequate medical treatment it should be much less (Carré *et al.*, 1952).

Symptomatic cure does not necessarily imply restoration to normal anatomical relationships. Astley (1956) found that symptoms usually disappeared at the time of weaning to solids, although often gastro-oesophageal incompetence could still be demonstrated. At first reflux might occur from the abdominal to the thoracic portion of the stomach, although little barium passed back into the oesophagus. Later reflux ceased at the level of the diaphragm. This suggested to him an initial improvement in the sphincteric power of the oesophagus, followed later by improvement in the 'pinchcock' mechanism.

Surgery. The outcome of surgical treatment in partial thoracic stomach in infants is not nearly so good as in adults. This is the opposite to what might be expected. In at least a proportion of infants it means that either the oesophagus is congenitally short so that the tendency for the stomach to herniate is too great; or that the diaphragmatic crura are abnormal and therefore unable to maintain the stomach in its normal position after surgical repair.

Associated Abnormalities. The simultaneous occurrence of partial thoracic stomach and other malformations have been reported (Williams, 1945; Radloff and King, 1947; Thomsen, 1955; Astley, 1956; Kohler, 1957). The significance of this association is doubtful but it has been suggested as corroborative evidence in favour of a congenital origin of thoracic stomach. There is no indication that infectious diseases during pregnancy, complicated labours or prematurity have any relation to this condition. The interesting association of hypertrophic pyloric stenosis and partial thoracic stomach is too common to be disregarded. Roviralta (1952) described this combination as the 'phrenopyloric syndrome'. Astley and Carré (1954) found five infants with pyloric stenosis as well as three other children with 'infantile pylorospasm' in a series of 115 cases with thoracic stomach. Forshall (1955) reported a series of 93 cases of 'cardio-oesophageal syndrome' in childhood in which eight infants were subjected to Rammstedt's operation. Four were irrefutable cases of pyloric stenosis. It has been suggested that herniation follows as a result of the stenosis. However, this is not true in most cases: vomiting is often present from birth; the hiatus is normal in cases of pyloric stenosis alone; and symptoms as well as the radiological appearance persist after division of the pyloric sphincter.

It is reasonable to conclude that sliding hiatal hernia in the adult is an acquired, degenerative condition that affects a normal hiatal region. Partial thoracic stomach in the infant is either due to a congenital short oesophagus or to herniation of the stomach through a congenitally malformed or undeveloped diaphragm. The relative frequency of each type is unknown. Despite statements to the contrary, it is impossible in the great majority of these cases to identify, beyond doubt, the 'congenital short oesophagus' or the 'hiatal hernia'; therefore the non-committal term 'partial thoracic stomach' is preferred.

Congenital Short Oesophagus

Tonndorf in 1923 postulated that thoracic stomach is the result of incomplete descent of the gastric organ due to failure of the oesophagus to elongate. During the fourth to seventh weeks of embryonic life, the oesophagus lengthens rapidly to keep up with the extension of the pharynx and the development of the lung buds (Botha, 1958a). If this elongation fails, the oesophagus will be partly or completely shortened. The stomach will lie somewhere in the posterior mediastinum, not because it has herniated to that position but because it has never descended into the abdomen, and it may therefore occur anywhere from the pharynx to the diaphragm. A case of extreme short oesophagus is to be published elsewhere (1958c) where the entire oesophagus consisted of a constriction of 2 or 3 mm. (Figs. 9 and 10). The stomach was in the neck, covered by peritoneum that stretched upwards like a funnel. The cardiac angle was obliterated. The poorly developed membranous diaphragm was tented up over the stomach and spleen. In the place of the hiatus was a huge, wide defect. Iniencephaly and cleft palate were also present. This maldevelopment of the diaphragm is secondary to insufficient lengthening of the oesophagus. This extreme degree of shortening, of which a previous description has not been found, must be relatively rare. More commonly the

FIG. 9.—The mediastinal organs and abdominal viscera of an iniencephaly which shows complete failure of the oesophagus to elongate. The spleen (S) lies in the chest enveloped by a thin serosal membrane.

FIG. 10.—The serosal membrane in the specimen in Fig. 9 is removed. The arrow indicates the oesophagus, a mere constriction between stomach and pharynx.

FIG. 11.—Partial thoracic stomach in an infant. The arrow indicates the 'empty segment', which is due to the contraction of the inferior oesophageal sphincter.

oesophagus extends to or below the level of tracheal bifurcation.

The oesophagus has remarkable powers of retraction. The organ may therefore shorten, after herniation of the stomach (as in a simple hiatus hernia), without any signs which might indicate its true length. It may become secondarily fixed in this position due to inflammatory changes which follow oesophagitis and ulceration; the shortening may be further aggravated by chronic fibrosis and scar contraction. Gastric mucosa is then present above the hiatus and the supradiaphragmatic loculus of stomach may in the course of years elongate to resemble the lower third of the oesophagus very closely. This well known clinical entity, which is not uncommon, is truly called 'short oesophagus' although it is not a 'congenital short oesophagus', a confusion of identity which has led to considerable misunderstanding. For this reason Tonndorf's conception fell into disrepute, especially after the papers of Johnstone (1943), Allison (1948) and others, so that later authors regarded congenital short oesophagus as a rare anomaly (Belsey, 1954; Thomsen, 1955 and Forshall, 1955). Certainly, many of the cases reported as congenital short oesophagus were really due to acquired shortening with associated hiatus hernia—described at a stage when the mechanism of hiatal herniation was imperfectly understood; but the diagnosis of congenital short oesophagus cannot be ruled out in the infant who vomits from birth and shows the following radiological features (Fig. 11): (1) A small, tubular, gastric loculus above the diaphragm; (2) a relatively fixed cardia above the diaphragm as evidenced by the distal border of the 'empty segment'. (This is due to the constriction of the inferior oesophageal sphincter and has been wrongly attributed to 'spasm' or 'stricture'). (3) A straight oesophagus; (4) obliteration of the cardiac angle; (5) a very wide, lax hiatus which may be tented.

The complete absence of oesophagitis in many infants with partial thoracic stomach entirely excludes any retraction or fixation due to chronic inflammatory scarring. Because oesophageal changes developed after one or two years in 'sliding hernia' where the gullet was normal before, Thomsen (1955) concluded that 'as is the case in adults, the shortening is due to reflux oesophagitis'. However, congenital short oesophagus necessarily implies that part of the stomach lies above the hiatus. As this deranged, insecurely fixed viscus is subject to all the forces that normally predispose to herniation, the loculus of stomach above the diaphragm may slowly increase in size. The normal closing mechanism is further disturbed, displaced and deprived of the important support of the crura. The reflux that follows leads to oesophagitis, fibrosis and more shortening. Thus 'congenital short oesophagus' and 'sliding hiatal hernia' may produce an indistinguishable end-result, and may co-exist.

Sliding Hiatal Hernia Due to a Malformed Hiatus

Instead of ascribing a primary inhibition of growth in the lower oesophagus (Tonndorf, 1923; Kelly, 1936; Lelong, 1947) as a cause for thoracic stomach, Bund (1918), Bailey (1919) and Åkerlund (1926) blamed the lack of fixation of the cardia on a persistence of the pneumato-enteric canal. This is considered unlikely because a relatively big thoracic stomach is sometimes seen at birth and even the biggest bursa should not allow this degree of mobility. Furthermore, little evidence of this peritoneal recess has been found at operation and the hiatus, which should be normally developed if the peritoneal sac is the only factor, is often abnormal. Harrington's (1940) theory that descent of the stomach is disturbed, with poor subsequent fixation to a wide hiatus, cannot be substantiated embryologically (Botha, 1958a). Shanks (1948) felt that the hiatus was congenitally enlarged, but the crural muscle was normal. Dunhill (1935 and 1948) described hiatal hernia with congenital absence of the left crus—the aorta bowed far to the left. Although this type of anomaly occurs it must be rare, and, relatively speaking, not an aetiological factor of clinical importance.

Bremer (1943) stated that hernia in the region of the tendinous antrum on the left side near the

oesophagus is less common than herniation through the trigonum lumbocostale. He thought it 'due to failure of the last step in the closure of the pleural passage, the growth above the descending stomach of the thin strip of liver and septal extension to join the mediastinum. Except for the large opening the diaphragm in this type is normal'. This writer's view on the development of the diaphragm cannot be accepted (Botha, 1958a) and no clinical or experimental evidence has been found to support his theory.

Numerous vague references to 'hiatal insufficiency' appear in the literature (Allison, 1948; Johnstone, 1943), but no satisfactory explanation has been advanced as to the cause of herniation in children. Forshall (1955) found at operation in 30 cases of partial thoracic stomach that the right crus invariably appeared poorly developed, especially the left limb and the posterior fibres. The diaphragm as a whole was often unduly thin, almost flaccid to the touch. She thought that a poorly developed hiatus is the congenital element of this sliding hernia in which the cardia is drawn through the hiatus by the difference in intra-thoracic and intra-abdominal pressures. Her operative findings, supported by the findings at operation of other workers, contrast so sharply with the normal anatomy of the crura that one must accept some congenital maldevelopment at the hiatus.

The nature of this abnormality is not yet known, but the following suggestions may be considered:

(1) Congenital absence of one or both crura is rare.

(2) Failure of muscularization of hiatal muscle so that a membrane forms at the site of the crura which envelops the cranial portion of the stomach (Christiansen, 1941). However, muscularization of the diaphragm begins in the 12 mm. embryo (Botha, 1957b), when the oesophagus has already become fully elongated and the stomach has reached its normal position. There is, furthermore, no selective failure of the muscle cells to invade the septum transversum so that the rest of the diaphragm must show signs of such an anomaly if it does occur. In any case, muscle fibres are easily demonstrated in the hiatal margins in cases of partial thoracic stomach at operation and necropsy.

(3) The wide hiatus, with no muscular defect. *X*-ray appearances certainly confirm the wide hiatus. It is difficult to understand though, why infants should be born with such a wide opening in the diaphragm and the rest of the anatomy normal. A study of the embryology and development definitely points against this theory. If the oesophagus is of normal length and such a big hole exists, one would expect a progressive, large, freely movable hernia; partial thoracic stomach is small and fixed. It is also unlikely that such a primary defective lax hiatus should later resume a normal function. Thomsen (1955) stated that 'hernia' in infants is not present at birth but only develops afterwards as a consequence of the change in pressure in the thorax and abdomen, and is due to a 'lacking or abnormal fixation of the cardiac region'. From what has been said before, this statement cannot be accepted.

Very large, mobile herniae are sometimes found where the oesophagus appears of normal length and they are quite unlike the usual case of partial thoracic stomach. Although it may only be a difference of degree, it is thought that these herniae are true sliders, probably in part due to either a poorly formed hiatus or atypical arrangement of the crura (Fig. 3 and 1d).

(4) Malformed hiatus secondary to congenital short oesophagus. When the oesophagus fails to elongate, the cardia is retained in the chest. The serosa is drawn out to this level and may form a membranous sac around the upper stomach. Crural development has been interfered with; the fibres are attenuated and underdeveloped; the crura are thin and the wide hiatus is tented upwards. In the very short oesophagus (Figs. 9 and 10; Christiansen, 1941, and many others) the phreno-oesophageal elastic and serosal attachment to the high cardia has attenuated the crura to an insignificant membrane-like covering. When the abnormality is minimal, a wide hiatus and poorly developed crura, as found at operation by Forshall, may be the only anatomical signs of abnormality.

Smithers (1945) found it 'difficult to believe that short oesophagus has nearly always been overlooked at post-mortem'. However, after spending some time in the necropsy room examining hiatuses of normal subjects as well as others with hiatus hernia, I fully sympathize and agree with Anders and Bahrmann (1932) and other authors on this subject; the degree of herniation is difficult if not impossible to assess after death.

It has been said that reduction of a partial thoracic stomach at operation refutes the diagnosis of a congenital short oesophagus. This is not necessarily true. The gullet not only possesses amazing qualities of retraction but also of extension. The hiatus in the adult may move as much as two and a half vertebral bodies during respiration (Botha, 1957b). At operation, with the patient in the supine position, the oesophagus is mobilized to 'above the aortic arch level' and pulled down while the diaphragm is completely paralysed by relaxants. The cardia, after reduction, is maintained in the sub-diaphragmatic position by approximating the crura and fixing the

oesophagus to the hiatal margin. This procedure might be impossible on inspiration or in the erect posture !

In conclusion, partial thoracic stomach is a relatively common disorder in infancy that might be due to congenital short oesophagus or a sliding hernia (or a combination of these conditions).

The two abnormalities cannot be distinguished in the majority of patients either by radiography or by endoscopy. I believe that a large proportion of instances of partial thoracic stomach are due to a congenital short oesophagus—a far greater percentage than has hitherto been recognized.

Para-oesophageal Hernia

Para-oesophageal herniae are uncommon. A portion of the stomach, usually the fundus, herniates through a relatively wide but otherwise normal hiatus while the cardia maintains its normal position. Cases in which the gastro-oesophageal junction has been displaced upwards, whether primary or secondary, cannot be regarded as true para-oesophageal types, but of a mixed variety. Para-oesophageal herniae are seldom present in infancy but usually occur later in childhood, adolescence or in the adult. They are always on the right side: left-sided ones are either of the mixed type or diaphragmatic. As the closing mechanism is acting in its normal position with optimum function, reflux and oesophagitis are unusual. However, this type of distortion frequently leads to ulceration, haemorrhage and even perforation.

The peritoneal sac which is commonly found is undoubtedly derived from the right pneumato-enteric recess (Åkerlund, 1926; Barrett, 1954; Botha, 1958a). Examples of these small empty sacs have been found on the right side as well as posteriorly, without any sign of herniation or any other abnormality around the hiatus. A large sac clearly invites early herniation, whereas the small ones remain as potential spaces which might later give way under strain. It then leads to a para-oesophageal hernia, a mixed hernia or it might weaken the attachment sufficiently to predispose to an ordinary sliding hernia with a sac. Harrington (1940, 1948) and Olsen and Harrington's (1948) views that these herniae, as with the sliding varieties, are due to congenital dilatation of the hiatus have not been verified.

Oesophagus Lined with Glandular Epithelium

Barrett (1950) first aroused interest in a condition which he called 'oesophagus lined by gastric mucous membrane'. Unfortunately this has been confused with congenital short oesophagus.

I have already indicated that some variation exists as to the level at which the squamous epithelium changes to glandular mucosa. In the adult, this variation is more marked and the level may occur anywhere from just below the cardia to the cricoid (Barrett, 1954). The epithelium is, however, not gastric epithelium, but glandular epithelium that closely resembles the 'zone of cardiac glands' in animals and man (Botha, 1958d). The tubules are short and tortuous; mucus-secreting alveoli are in abundance and oxyntic cells are either absent or very scanty. It is suggested that these glands represent a more primitive epithelial cell type, which, for one or other reason, has not fully differentiated into squamous epithelium (Botha, 1958d). There is evidence that these aberrations might predispose to oesophagitis and ulceration (Allison and Johnstone, 1953). Normally this condition has no relation whatsoever to short oesophagus or hiatus hernia. It might, however, be present in the lower oesophagus of a patient who later develops a hernia or it might line the lower portion of an oesophagus that is congenitally short, but it is then unusual and purely coincidental. Some of the cases reported as of gastric-lined oesophagi are actually cases of hiatal hernia or congenital short oesophagus where the cardia lies well above the diaphragm. One of the main reasons for this misconception is the view held by some workers that the squamo-glandular junction is the dividing line between stomach and oesophagus. If this is used as a standard, some animals will either possess an oesophagus and no stomach or others will only have a stomach without a gullet (Botha, 1958d). The site at which squamous and glandular epithelium meet cannot be regarded as the dividing line between stomach and oesophagus in man; it so happens that in the vast majority of people it takes place at or near the cardia.

Cardio-oesophageal Relaxation or 'Chalasia'

Neuhauser and Berenberg in 1947 reported 12 infants with 'persistent vomiting evidently due to relaxation or dysfunction of the hiatus portion of the esophagus with failure of the normal "sphincter" action of the cardia'. They called this 'cardio-esophageal relaxation or chalasia'. With conservative treatment symptoms disappeared after a few months and the infants showed no physical or fluoroscopic abnormalities. It was thought to be a temporary neuromuscular dysfunction of the hiatus portion of the oesophagus and diaphragm (Berenberg and Neuhauser, 1950). Forshall (1955) preferred the term 'lax oesophagus', because 'it is not only the cardia which is relaxed but also the whole lower two-thirds of the oesophagus'. However, it has been shown that the lower oesophagus in normal

infants is characteristically wide, readily distensible and even sac-like on occasions, with irregular contractions and contours (Lelong and Aimé, 1934; Bakwin, Galenson and Le Vine, 1944; Thomsen, 1955; Henderson, 1942; Malenchini, Roca and Banzas, 1948).

There are other reasons why this condition is not likely to be a neuromuscular imbalance: the hiatus is usually wide and lax though there is no obvious autonomic connexion with the phrenic nerves or the diaphragmatic crura (Botha, 1957a). The cardiac angle is lost (Forshall) and the cardia itself appears on a higher level than normal, as if it has been ' drawn up ' into the hiatus. Drugs have no effect on this condition but recovery is remarkable in the great majority by nursing in the sitting posture. In adults, the level of the diaphragm as seen radiologically does not necessarily correspond to the level of the hiatus (Botha, 1957b). This is probably true in children, to a lesser degree, which makes it impossible to say with certainty that the cardia is below, at, or above the hiatus. One knows that in at least some of these cases, partial thoracic stomach later develops (and not necessarily associated with oesophagitis). Post-mortem and operative findings cannot be regarded as reliable. The radiological appearances are often extremely difficult to interpret and one may still be uncertain as to the diagnosis even after several examinations (Astley and Carré, 1954).

I believe that patients with 'chalasia' really suffer from mild degrees of partial thoracic stomach, but instead of the cardia being clearly in the chest, it is lying in or just above the hiatus. This slight distortion is sufficient to render the normal closing mechanism incompetent. Some deteriorate into sliding herniae. The great majority are treated medically in the sitting posture with permanent cure. Gravity assists the descent of the cardia to its normal position and thus normal competence is re-established.

Summary

The anatomy of the gastro-oesophageal region in more than 115 infants and children has been studied. The outstanding features were: a small powerful hiatus with marked overlap and an oblique lengthy tunnel; a formidable phreno-oesophageal membrane and secure fixation of a narrow terminal oesophagus. These features were considered to be mainly responsible for the superior gastro-oesophageal competence in infancy. In contrast, hiatus hernia in the elderly is a terminal degenerative manifestation in the evolution of the cardiac region.

Differences in age, sex and familial incidence, clinical course, radiological features, associated abnormalities and in the outcome of surgery support the view that the mechanism of partial thoracic stomach in infancy and hiatus hernia in adults are not identical conditions. The noncommittal term 'partial thoracic stomach' is preferred as it is impossible in the great majority of cases to distinguish between sliding hiatal hernia and congenital short oesophagus.

Evidence suggests that a large proportion of cases of partial thoracic stomach are due to congenital short oesophagus.

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PAEDIATRIC SOCIETIES IN THE BRITISH ISLES

The following is a list of paediatric societies and their principal officers at the time of compilation. Alterations when they occur, information on new societies or any omissions from this list should be passed to the Secretary of the British Paediatric Association.

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British Paediatric Association
President: Dr. K. H. Tallerman
Secretary: Dr. P. R. Evans
Institute of Child Health,
The Hospital for Sick Children
Great Ormond Street,
London, W.C.1.

The Royal Society of Medicine, Section of Paediatrics
President: Dr. A. Doyne Bell
Secretaries: Dr. Trevor P. Mann
H. H. Nixon, F.R.C.S.
The Royal Society of Medicine,
1, Wimpole Street,
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The British Association of Paediatric Surgeons
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Secretary: R. B. Zachary, Esq., F.R.C.S.
Children's Hospital,
Sheffield.

The Scottish Paediatric Society
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Department of Child Health,
Medical School,
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Scottish Surgical Paediatric Club
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Secretary: Wallace M. Dennison, Esq., M.D., F.R.C.S.(Ed.), F.R.F.P.S.G.
Department of Paediatric Surgery,
Royal Hospital for Sick Children,
Glasgow, C.3.

Paediatric Pathology Club
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Ulster Paediatric Society
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Irish Paediatric Association
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Secretary: Dr. Raymond Rees
18, Fitzwilliam Square,
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Department of Child Health
Llandough Hospital,
Penarth, Glam.

II: Regional

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Secretary: Dr. John Apley
Children's Hospital,
St. Michael's Hill,
Bristol, 2.

The Liverpool Paediatric Club
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Secretary: Dr. R. McL. Todd,
Department of Child Health,
Alder Hey Children's Hospital,
Eaton Road,
Liverpool, 12.

Paediatric Society of the South-East Metropolitan Region
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16 Ferncroft Avenue,
London, N.W.3.

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374, Great Western Road
Aberdeen.

Caernarvonshire and Anglesey Paediatric Club
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12, Montpelier Row,
Blackheath, London, S.E.3.
Chairman: R. H. Percival, Esq., F.R.C.S.

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St. Mary's Hospital,
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The Children's Hospital,
Ladywood Road,
Edgbaston,
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Sheffield Regional Paediatric Society
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58, Nether Edge Road,
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"Hillcrest",
Farnley Hey Road,
Durham.

BOOK REVIEWS

Congenital Anomalies of the Viscera. By J. L. BREMER. (Pp. ix+202; 98 figures. 40s.) Harvard University Press (London: Oxford University Press). 1957.

The author is breaking new ground in attempting to give in book form a reasoned explanation, based on the embryology of the parts, of congenital visceral anomalies. His intention is to supplement the knowledge of human development usually gained by a medical student, and to show how slight variations in the timing of events, or changes in the relative positions of structures, lead up to many of the congenital malformations found in paediatric practice. The author gives a clear, succinct, and, at times, a very revealing account of the normal events, although some of the generalizations necessary in such a summary will not be unequivocally accepted by all embryologists as valid for human development. The normal development of each organ or system is first reviewed before the anomalies of that part are discussed. In this way the reader can readily follow the significance of variations from normal developmental sequences. Anomalies of the brain and spinal cord are omitted, except in so far as they are associated with anomalies of other viscera, as forming too vast a subject for a book of this compass. The face, the respiratory and the alimentary systems are dealt with in the first five chapters; the urinary system and suprarenals, and the male and female genital apparatus in the next two; while the heart and great vessels are considered in the four remaining chapters. The only serious omission of a common anomaly noted is that in which the apex of the developing lung is split by the right common cardinal vein, to give rise to the 'lobe of the azygos vein' in the fully formed state. It is surprising to find the statement (p. 55) that Hirschsprung's disease 'is due to no intrinsic maldevelopment or disease of the colon itself, but to a malfunctioning or stenosis' of the bowel below the dilated portion. Bodian, Stephens and Ward (1949) clearly demonstrated that a congenital absence of ganglion cells from the intramural plexuses of the narrowed distal colon is the underlying cause of the malfunctioning of the bowel in this condition.

The emphasis on alimentary and cardiovascular anomalies produces a certain imbalance in the book. The work of Barr and subsequent investigators on the sex chromatin of the female cell nucleus, and the fascinating problems of intersexuality have not been discussed. In view of the present very great interest in anomalies of the sex organs, and of the associated hormonal and chromosomal derangements, this is greatly to be regretted. These remarks are not intended in any way to detract from the many and brilliant explanations of visceral abnormality based on the logical follow-up of slight variations in the normal mechanics of development. Rather it is a matter of regret that an author, so well equipped to deal with the variations of human development, has failed in some degree to give an adequate lead in suggesting possible fundamental causal mechanisms for structural defects, or to integrate the newer knowledge of biochemical and hormonal factors which influence growth mechanisms, into the fabric of the book.

The book as a whole is beautifully set out and a pleasure to read, so that misprints, when they occur, are all the more noticeable. 'Sphincter', for example, is misspelt twice (pp. 121, 123), and 'patten' becomes 'pattern' (Fig. 12). It is inferred (Fig. 89) that rats remain in the embryonic condition for seven weeks, although the gestation period for these animals is only three weeks. Apart from such relatively unimportant faults as these, the book is to be highly commended to all seeking a clear account of the embryological basis of congenital visceral anomalies.

Bodian, M., Stephens, F. D. and Ward, B. C. H. (1949). *Lancet*, **1**, 6.

The Mentally Ill Child: A Guide for Parents. By STEVEN B. GETZ and ELIZABETH LODGE REES. (Pp. xiv+88. 25s.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1957.

A book of this kind was certainly needed, for the problem of the mentally ill or psychotic child is still very imperfectly understood. It is important that those in administrative charge of children, school medical officers, doctors in infant welfare clinics, and so on, should be able to distinguish psychosis from mental defect.

This book, however, is written for parents, and for American parents at that. For the English parent inevitably much of the information about certification and placement is inappropriate to this country. A worse fault is that the book contrives to leave a confused effect; the description of the child could have given some explanation of his needs, rather than describing them in a catalogue, and the very difficult problem of relationships within the family containing a mentally ill child is discussed at a quite superficial level.

The bibliography, of 10½ pages, is a full one (with a few rather surprising omissions), but is mainly a bibliography for the professional reader. It would certainly startle a conscientious parent who embarked on it.

It is to be hoped that the success of the parents' association for children of this kind, which has been formed in America, may lead to something similar in this country. For these are children for whom administrative provisions are woefully inadequate, and who are often too sick to remain at home, too disturbed for the child guidance clinic and who tend to be relegated to occupation centres and hospitals for the mentally defective because no other provision is possible.

PRO-BANTHĪNE* IN ULCER HEALING

FIG. 1. *" But X-ray study at this time still revealed the ulcer niche."*

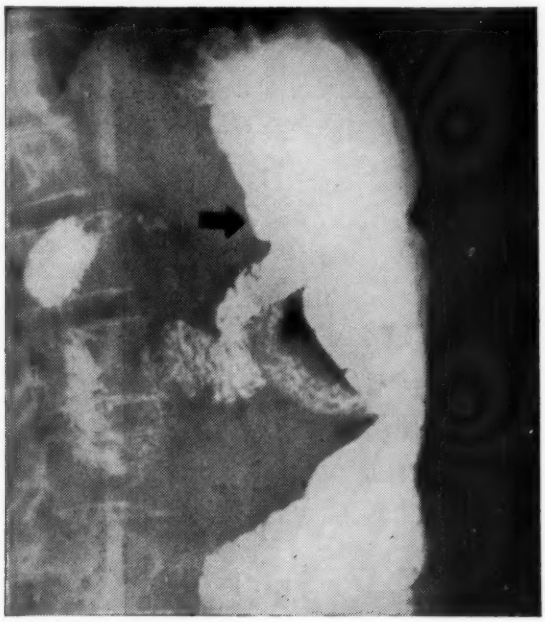

FIG. 2. *In ten weeks " the niche was no longer visible radiologically or gastroscopically."*

Clinical Report on Pro-Banthīne

The case-history below of ulcer on the gastric side of gastro-jejunal stoma reveals significantly the high potency in low dosage of the well-tolerated anti-cholinergic agent, Pro-Banthīne.

M. D., female, age 48, had a posterior gastro-jejunostomy fourteen years previously for duodenal ulcer. Nine months prior to her first visit severe intractable pain recurred and a subtotal gastrectomy was performed at another hospital. She remained well for a few months and then because of recurrence of severe pain and marked weight loss, she was referred for treatment. X-ray study revealed a large ulcer niche on the gastric side of the anastomosis. Antacids and sedatives gave no relief from pain. She was given 45 mg. of Pro-Banthīne four times a day and within seventy-two hours was able to sleep through the night for the first time in weeks. After two weeks of Pro-Banthīne treatment the patient felt completely well, but X-ray study at this time still revealed the ulcer niche (Fig. 1). After a further ten weeks' treatment the niche was no longer visible radiologically or gastroscopically (Fig. 2). In the five months prior to the report she was maintained on 30 mg. of Pro-Banthīne four times daily without any recurrence of symptoms.

Pro-Banthīne is the safe, potent anti-cholinergic agent which effectively controls excessive parasympathetic activity in the gastro-intestinal and genito-urinary tracts.

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PB : P97

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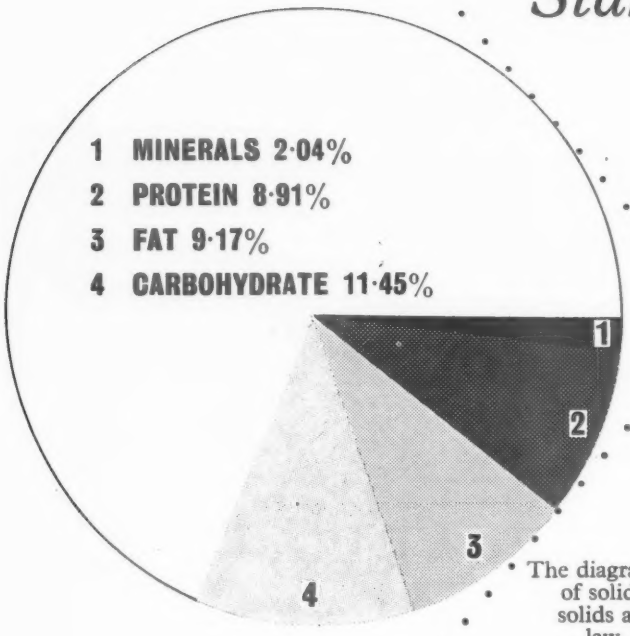

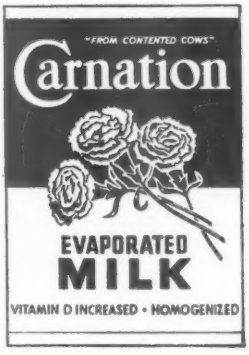

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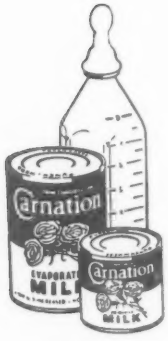

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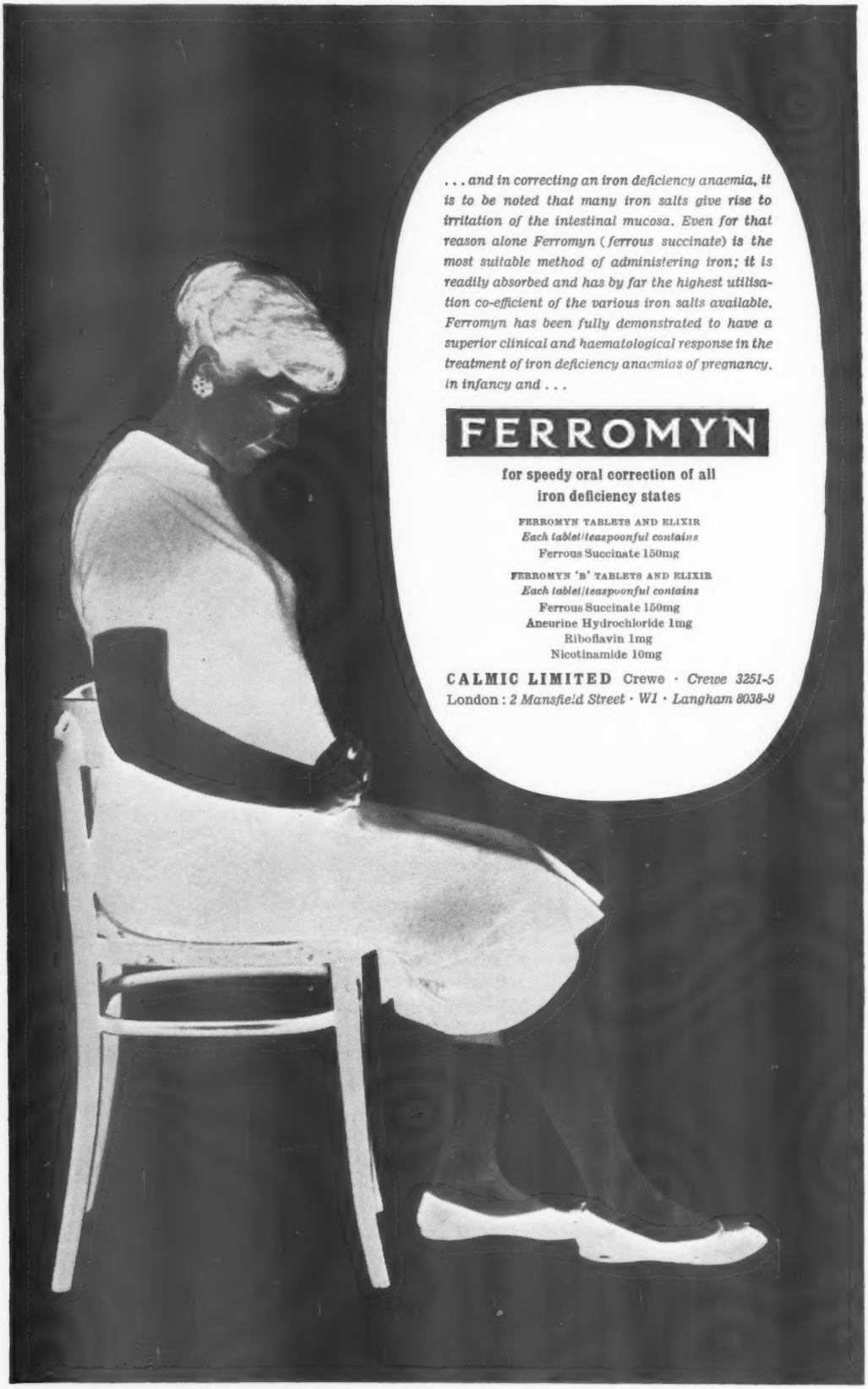
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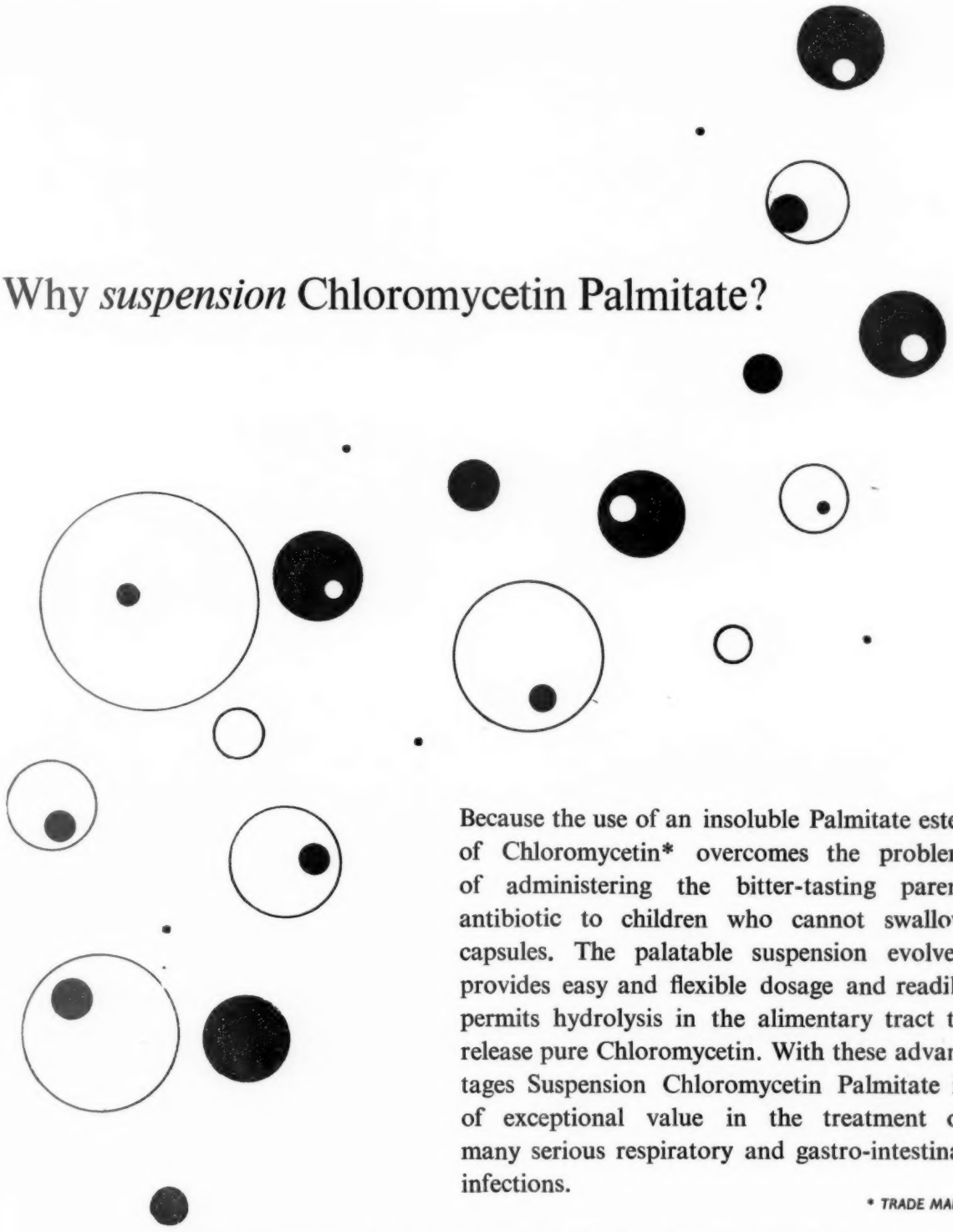

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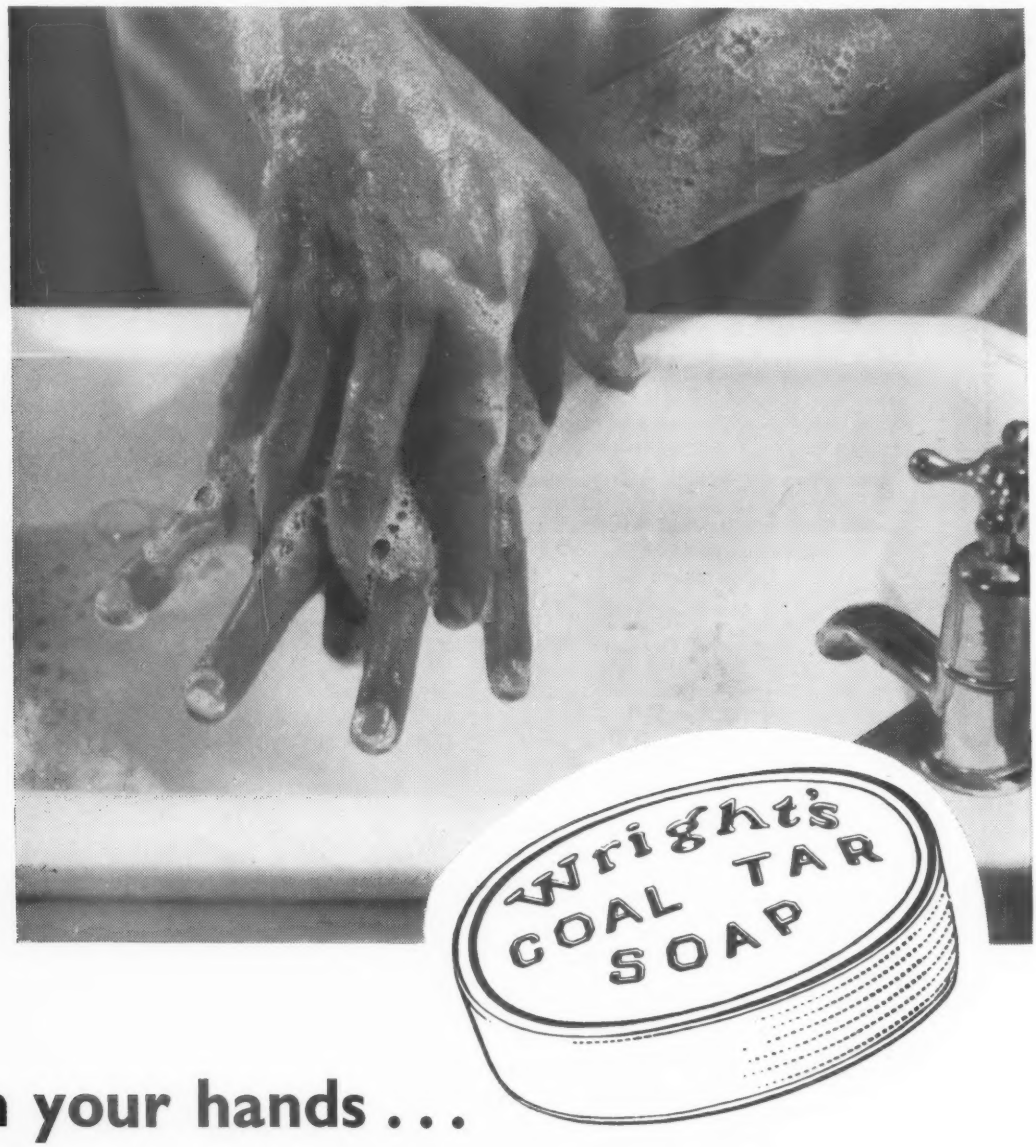

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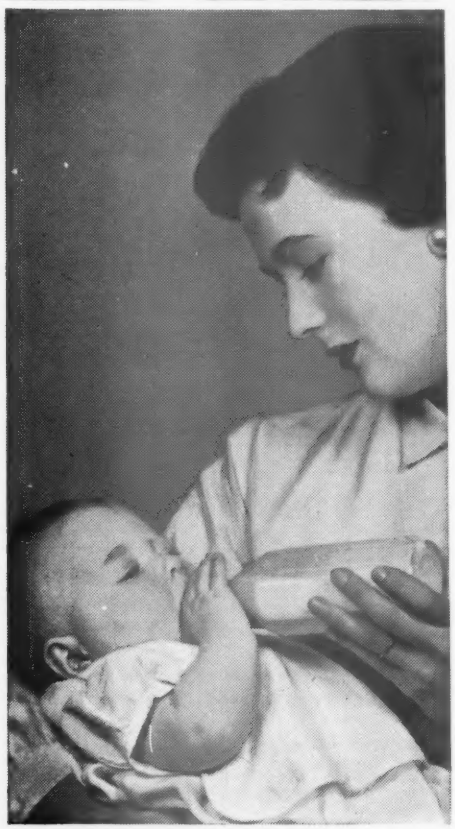

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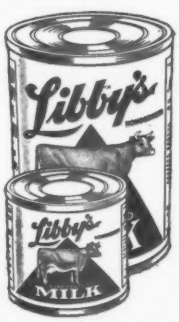

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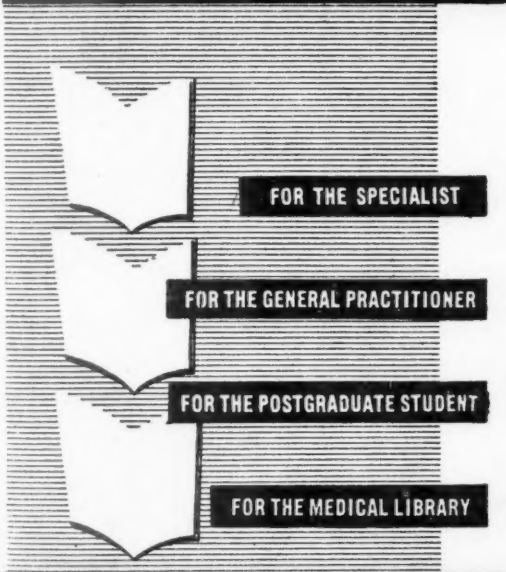

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